The New England
Journal of Medicine

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Volume 230 MARCH 23, 1944 Number 12

THERAPY WITH FEMALE SEX HORMONES*

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THIS paper is concerned for the most part with functional disorders, since it is almost exclusively in these that hormones are of value. The use of the term "functional" is an admission of ignorance concerning the actual cause and mechanism of a given disability. Irregularities of living — namely, faulty diet, insufficient rest, inadequate healthy activity, changes of environment, strained social relations, absence of healthful routines, shocking episodes, poor emotional adjustment, psychic disturbance, ill-suited occupation, bad habits and so forth — are often obviously, and apparently causally, associated with all sorts of functional disturbances of the various bodily systems for which no organic basis can be ascertained by available methods of study and diagnosis. It is therefore reasonable to assume that these irregularities of living may be more or less involved in the development of gynecologic functional disorders, and indeed careful inquiry often reveals that such is probably the case. Fortunately, many functional upsets are likely to be temporary because they either force the patient to mend her ways spontaneously or to consult some physician who points out her errors of living and the means of correcting them. With exceptions, prescribed and voluntary adjustments of living and constitutional changes over a period of time have more to do with curing patients than has the therapy administered specifically for the complaint. The therapy presumably tides the patient over and sets the stage for cure.

FUNCTIONAL DISORDERS OF MENSTRUATION

Before taking specific steps concerning the patient's presenting complaint, four things should be done. First, well-recognized causes of manifestations similar to those of functional origin must be ruled out. These include amenorrhea due to or associated with congenital anomalies; systemic infections; wasting disease; diabetes; hyperthyroidism; ovarian, adrenal and pituitary tumors; Cushing's and Fröhlich's syndromes; Simmonds's disease and anorexia nervosa; dysmenorrhea due to pelvic inflammation; endometriosis, adenomyosis and tumors; abnormal genital bleeding due to pathologic pregnancy, cancer, polyps, tumors, inflammations, endometriosis or blood dyscrasias; and sterility due to inflammations, anomalies, endometriosis and tumors; and pathologic entities in the male. Second, the patient should be advised concerning better living habits — those of elimination, rest, activity and occupation — and the adjustment of social problems. Third, the proper medication, such as sedatives, iron and thyroid, should be recommended. Lastly, the elimination of focal infections should be seen to. Prescribing thyroid for patients with the disabilities outlined is more a matter of art than of science. The value of such treatment cannot be measured in terms of the basal metabolic rate and the blood cholesterol alone. Most of those who are studying and treating patients with pelvic symptoms and signs of dysfunction rely on it as a basic part of therapy and are convinced of its value, although it is impossible to explain the mechanism of its effect.

If menstruation does not begin before the age of sixteen, a diagnosis of *primary functional amenorrhea* should be considered, general examination and indicated studies performed, and general treatment begun, as outlined above. If no menstruation occurs by the age of eighteen, this diagnosis is reasonably certain, and efforts at specific treatment may be undertaken. That the amenorrhea is indeed functional can be determined only by demonstrating fundamentally normal genitalia. Without abdominal exploration the diagnosis remains presumptive. Performing an operation simply to prove that the cause is not absent or rudimentary ovaries is hardly warranted. Since there is no tangible benefit to the patient by operation, it seems better to assume that the amenorrhea is functional until the passage of time and the failure of treatment indicate otherwise. Primary and presumably functional amenorrhea is not associated with any other

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 11, 1943.

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unequivocal stigmas of endocrine imbalance. It occurs in normal young women in whom uterine bleeding can be artificially induced.

Secondary or acquired functional amenorrhea, by definition, means that uterine bleeding has previously occurred. That it is not likely to be permanent is attested by the small number of patients seen with this complaint between the ages of thirty and forty. It is unassociated with any other clear stigmas of endocrine imbalance.

An immediate or possible future desire for pregnancy is the main reason for treating patients complaining only of amenorrhea, and in this group may be included those with delayed, skipped and scanty periods. Ovulation is the ultimate aim, although the psychologic value of induced simple bleeding may be great. Unfortunately, ovulation as an immediate result of available therapy cannot yet be promised, but with persistent treatment and the passage of time it may be reasonably expected.

The following treatment is suggested for patients with amenorrhea. Give 1 mg. of diethylstilbestrol orally daily with breakfast for thirty-five days, and 10 mg. of progesterone intramuscularly daily for the following five days. Two to five days after the last injection, a two-day to five-day flow will probably ensue. Counting the beginning of flow as the first day, give 0.5 mg. of diethylstilbestrol daily from the fourth through the twentieth day, and 10 mg. of progesterone intramuscularly daily from the twenty-first through the twenty-fifth day. A period will probably occur around the twenty-eighth day. Repeat the last two steps twice, and then again twice, but reduce the diethylstilbestrol to 0.3 mg. daily. After the next period, give the usual course of diethylstilbestrol daily but omit the progesterone. By that time a spontaneous flow may occur and recur at regular intervals on 0.3 mg. of diethylstilbestrol taken daily, except during flowing. If there is no flow by the thirtieth day, give the progesterone series again.

If after one or more trials with the above schedule of treatment no spontaneity of flow is discernible, it is reasonable to assume that the patient has some basic irremediable defect and that nothing further is to be gained. This therapy is worth trying in patients with Fröhlich's syndrome.

For patients with delayed, skipped or scanty periods, give the treatment described above for the fourth to the twenty-fifth day, and repeat it as seems desirable. So often do these patients have premenstrual distress or tension that this program will be found especially salutary.

Presumably because of variations in intestinal absorption, the orally active anhydro-hydroxyprogesterone cannot be counted on as an effective substitute for injected progesterone. Neither may chorionic, pituitary or pregnant-mare-serum gonadotropins be expected to give predictable results in the above conditions or in the disorders to be discussed below. Undesirable reactions frequently follow the injection of such preparations. Furthermore, the gonadotropins of animal origin are likely to become ineffective from inducing acquired immunity. The rationale of the above program of treatment is based on the fact that the ovarian steroids have retroactive effects on the anterior hypophysis and that administering them so as to induce cyclic flowing seems to regulate pituitary gonadotropic activity when it is present. It is probable that better regulation would be accomplished if real postovulatory-like menstruation could be produced, but to do this is still impractical owing to the cost of progesterone and the inconvenience of more injections. Recent reports indicate that estrone sulfate (Premarin) may be a more satisfactory oral estrogen than diethylstilbestrol, 2.5 mg. of the former being equivalent to 1 mg. of the latter.

Dysmenorrhea

No clear-cut program for the management of essential, primary or functional dysmenorrhea can be outlined. There are too many variables. Each case presents a different and special problem. Too often have both good and poor results followed exactly similar treatment. If the disability is sufficiently disturbing, a properly executed presacral neurectomy is at present the only means of achieving a cure.

Dysmenorrhea cannot be *cured* by hormones. Temporary relief has been obtained with trials of all the available sex hormones given at various times in the cycle and in various amounts, but the results have been unpredictable and hence not consistently confirmable.

If in the course of managing a case according to one's preference a trial of hormones is elected, predictable although limited benefit may be obtained by the following procedures.

The first of these is to inject 2.5 mg. of estradiol dipropionate intramuscularly on the fifth, eleventh and seventeenth days after the beginning of a period, which prevents the next expected period from occurring. A painful menses usually starts forty-eight to fifty-six days from the onset of the last catamenia. By this technic, half the patient's painful periods can be eliminated.

The second procedure is to give 1.0 mg. of diethylstilbestrol orally daily for twenty doses, beginning twenty-four to seventy-two hours after the onset of menstruation. This is usually followed by a painless flow at approximately the expected interval. Occasionally the expected painless flow fails to appear and in another three or four weeks a painful menses occurs. This treatment, which was worked out by Sturgis,* can be counted on to give complete relief in two out of three cycles. Its main drawback is that not all patients can tolerate the

*Sturgis, S. H. Use of stilbestrol in relief of essential dysmenorrhea. *New Eng. J. Med.* 226:371-376, 1942.

drug, which must be taken as prescribed to produce the desired effect. Diethylstilbestrol also causes vaginal discharge through stimulating the secretion of cervical mucus. It should be employed only as a temporizing measure and not indefinitely.

The third procedure is to administer the male sex hormone, testosterone. This substance is considered by many to be also a female sex hormone. Its place in gynecologic treatment is not yet settled. Some are averse to its employment; others are convinced of its safety and value in the functional disorders of women. My experience with it has been too small to allow an expression of opinion. Relief in about 70 per cent of patients with dysmenorrhea has been reported following various methods of administering testosterone, the simplest being the ingestion of 20 mg. of methyl testosterone daily for fourteen days beginning on the twelfth day of the cycle.

It is evident that alleviation of dysmenorrhea by hormones depends on sufficiently upsetting the patient's own endocrine balance. Hormone therapy, however, does no immediate or permanent harm.

Functional Uterine Bleeding

It is in patients with this disorder in its various manifestations that thyroid is especially beneficial and sometimes apparently curative. Doses approaching tolerance may have to be given.

For those whose catamenias come at approximately twenty-eight-day intervals and are profuse or prolonged or both, 10 mg. of progesterone and 1 mg. of estradiol benzoate (or dipropionate), should be injected simultaneously intramuscularly on the twenty-first day and followed on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly. Three cycles of this therapy are usually sufficient.

For the patient whose otherwise fairly normal periods are occurring at too frequent intervals, the previous procedure should be followed, beginning the injections eight days before the anticipated onset of flow and continuing them until the cycle lengthens.

For the patient who is having continuous flowing, 10 mg. of progesterone and 1 mg. of estradiol benzoate should be injected intramuscularly at once and 10 mg. of progesterone daily for the next four days. During this time the bleeding will probably decrease or cease. Two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, these injections should be repeated beginning on the twenty-first day. Treatment in this manner should be given at least twice, and it may be required again after a lapse. If the patient is bleeding profusely, rapid control is obtained by raising the daily amount of progesterone to 50 mg., reducing the dose as soon as bleeding is less, but in any event continuing injections for five days or even longer until the bleeding stops or becomes minimal. There will follow the usual hormone-withdrawal flow and then a remission. Cyclic therapy should be continued as described above. At that point the cost of the advocated amounts of progesterone demands consideration. The objection that such therapy is of prohibitive cost may be countered by the fact that progesterone is a true female hormone, effective if given as prescribed, and that its price is being reduced.

For the patient who has a number of days of staining before the catamenia actually begins, the first procedure should be followed if treatment seems desirable.

Marked secondary anemia does occur but is unusual in women with functional flowing. Oftener it intimates the presence of a submucous fibroid, a placental polyp or a subinvoluted placental site. Submucous fibroids have occurred so frequently in patients whose anemia seemed out of all proportion to the amount of described and observed flowing as to make one suspect that they may somehow be the cause of the development and absorption of some hemolytic agent. When operation for fibroids with bleeding cannot be immediately undertaken because of undue risk, testosterone propionate in doses up to 75 mg. intramuscularly weekly may be tried, with expectation of some success if a submucous fibroid is not present and of less success if one is present. This hormone is now considered by many to be of value for patients with hypertensive and arteriosclerotic cardiovascular disease. It may come to be a part of the preoperative preparation of such patients when a submucous fibroid necessitates surgery.

The hormonal treatment described is satisfactory for women before they reach their premenopausal years. Examination under anesthesia, diagnostic curettage — followed by careful exploration with a placental forceps, which may catch the polyp missed by the curet — and cervical and endocervical biopsy must, of course, often be performed before the diagnosis of functional flowing becomes clearly acceptable. A burning desire for pregnancy and extreme fear of an induced menopause are the only conceivable reasons for temporizing with the use of hormones in cases of disturbing functional flowing after the age of forty-two. Diagnostic procedures under anesthesia are practically always mandatory, and sterilization by radium at the same time is simple and effective. In fact, the increased safety of major pelvic surgery and the present-day apprehension concerning pelvic cancer, based on the frequent finding of disturbing pathologic changes — anaplasia and areas suggestive of early neoplasia — in the endometriums and cervices of patients in the fifth decade, and on the insidiousness of adnexal cancer, are at present inducing a preference for hysterectomy and castration to radiation in this age group, especially if there is any other indication for surgery and no forbidding contraindication.

Unfortunately, pelvic cancer has developed often enough at a later date in patients sterilized by radium or x-radiation to demonstrate that this therapy should not be considered prophylactic against cancer.

Disorders Associated with Menstruation

Premenstrual Tension

Premenstrual tension or distress of minor degree is almost universal. Most women are aware of or at least evince by their conduct some of the following troubles to a greater or less degree: premenstrual irritability, apprehension, depression, mental confusion, dizziness, emotional instability, decreased efficiency, easy fatigue, headache, sense of tightness of the head ("head all tied up with iron strings," as one patient recently described it), nasal congestion, sense of abdominal fullness, backache, pelvic discomfort, aching of upper thighs, chilly sensations, swelling and soreness of the breasts, hot flushes and even localized or diffuse edema. When these troubles are disturbing enough, they are considered a clinical entity and given the above appellation.

Since premenstrual tension is more frequent and more severe after the age of thirty-five than before it, the simplest explanation is that it results from the decreased efficiency of aging ovaries in their balanced production of estrogen and progesterone. According to this point of view, it is essentially a part of the climacteric during the premenopausal years, and when it occurs in young women it may be interpreted as a premenstrual imbalance of the ovarian hormones.

The treatment suggested for this condition is to give 0.3 mg. of diethylstilbestrol orally with breakfast daily through the cycle. If relief is adequate, a dose of 0.2 mg. daily may be tried. After three months, treatment may be interrupted temporarily or permanently. No endocrine therapy has yet been worked out for those rare cases of clinically apparent premenstrual and menstrual edema.

Headache

Headache associated with menstruation is often a complaint of patients who are sooner or later found to have endometriosis. In the absence of confirmatory symptoms, signs and findings of this disease, nonincapacitating headaches may be considered and treated as part of the premenstrual tension syndrome. When, however, headaches associated with menstruation are incapacitating, resemble migraine, and yet are not controlled by ergotamine tartrate, the best treatment at present is the intramuscular injection of 1 mg. of estradiol dipropionate seven days before the expected onset of the catamenia.

Mammary Pain and Secretion

Any hormone treatment for breast complaints is emphatically to be restricted to those whose breasts are engorged, thickened or diffusely nodular. All thought of endocrine therapy must be dispelled when a discrete mass, cystic disease or bloody secretion is encountered. These are surgical problems, with the exception of some cases of cystic change in the breasts of young women. (I recently cared for a patient with a painful cancer of the breast and axillary metastases who had been treated for three months by hormone injections and "ovary tablets.")

The simplest remedy for premenstrual soreness and swelling of the breasts is diethylstilbestrol, 0.3 mg. daily, reduced to 0.2 mg. daily as soon as relief is experienced. Some patients have chronic intermittent bilateral breast pain with premenstrual exacerbation. They are likely to be disturbed mentally, with a "breast fixation." These cases are rare. Testosterone propionate is reported to be effective, and 30 to 50 mg. is given intramuscularly weekly, beginning twelve to fourteen days before the expected period, or even through the month except during flow, for two or three cycles. Re-treatment is usually necessary after one or more months' rest from injections. Delayed periods may occur when male hormones are given during the first sixteen days of the cycle.

The management of patients with nonbloody mammary secretion is still unsettled. Secretion indicates cystic change. When to operate and how much tissue to remove are the problem. In older women simple mastectomy is the easiest solution. Unless all breast tissue is removed, periodic examination for an indefinite length of time is mandatory. In young women the secretion may be temporary, as may the cyst if it is palpable. Mammary secretion, with or without pain, in those for whom surgery does not seem necessary is said to be controlled by testosterone propionate, given as for those with painful breasts.

Midmonth Pain or Bleeding

Functional midmonth pain or bleeding is not a frequent or persistent disturbance. Thyroid is the simplest medication. Methyl testosterone, 5 to 10 mg. being given orally daily, except during menstruation, for three to five months, is said to hasten the disappearance of this ovulation syndrome.

The Menopause

Diagnostic pelvic investigation under anesthesia for postmenopausal uterine bleeding has been more frequently required since diethylstilbestrol became the generally preferred estrogen for the treatment of the climacteric. In addition to the trouble and expense entailed by this development, these patients must be followed with special care to be sure that the flowing did indeed result from the medication, for even after careful examination under anesthesia and findings consistent with hormonal bleeding, one cannot avoid a feeling of uncertainty regarding the possibility of adnexal or intramural

neoplasm. Keeping the daily amount of diethylstilbestrol below 0.5 mg. avoids induced endometrial bleeding and practically always suffices for the control of menopausal symptoms. It is worth while remembering that painful joints are frequently a menopausal symptom that responds rapidly to small amounts of estrogenic substance.

Functional Sterility

Once the husband has been shown to produce a healthy semen and the wife to have a healthy vagina and cervix, palpably normal internal genitalia, patent tubes, regular menstruation from a secretory endometrium and endocervical mucus containing a fair number of active spermatozoa three to six hours after intercourse, failure to conceive may be considered functional. In these situations, general health measures, as outlined earlier, small doses of thyroid and mild intrauterine trauma or tubal insufflation within a few hours after intercourse at about midcycle every two to three months are likely to be effective without the use of sex hormones. During the last year 3 women with functional sterility became pregnant one to six months after I had temporarily given up hope of success, having for the previous twenty-four to thirty months followed the above recommendations and in addition having employed various hormones in carefully planned trials. This sort of experience makes me diffident about offering advice, and philosophic in my attitude toward the treatment of functional sterility. At the Free Hospital for Women it has been believed for some years that the daily ingestion of moderate doses of an estrogen enhances the wife's chances of pregnancy, and 0.1 to 0.2 mg. of diethylstilbestrol is now commonly prescribed. A study of the literature indicates that there is as yet no specific hormonal means of increasing fertility in the husband. For him the best treatment appears to be an active out-of-door vacation, in addition to general health measures and the giving of thyroid.

Functional sterility sometimes exists because the wife is having anovulatory cycles, as indicated by failure to find secretory endometrium on biopsy at the beginning of flow, in which case injections as described above in the first procedure under "Functional Uterine Bleeding," should be given until a secretory endometrium is found.

Miscellaneous Conditions

Frigidity

Methyl testosterone, 10 to 20 mg. orally daily, has been reported as effective in those women whose desire for and satisfaction from intercourse have waned. This medication is also stated to render them more stable emotionally and to make them feel more energetic.

Vaginitis and Pruritus, Kraurosis and Leukoplakia of Vulva

It is customary in reviews like this to describe the use of hormones in these conditions, but there appears to be no routine need for them. Vaginitis usually responds to mechanical cleansing and simple antibacterial and antiprotozoal remedies. Rarely it is necessary to resort to the daily vaginal insertion of 0.5 mg. of diethylstilbestrol for a persistent senile vaginitis.

Pruritus responds to dermatologic treatment if it is due to bacterial and fungus involvement and if the process is superficial. If the process involves the deeper layers of the vulva, and especially if it is localized in the vulval tissues, complete superficial vulvectomy is usually sooner or later necessary. Kraurosis and leukoplakia are likely to require surgery. The histologic changes of lichen planus of the vulva are similar to those of kraurosis and leukoplakia. If lichen planus is sufficiently localized and the irritation from it is not relieved by conservative means, surgery is justifiable.

* * *

For years, of course, the treatment of functional gynecologic disorders has consisted of general health measures, the giving of thyroid and of ovarian extracts and the care of associated conditions, such as anemia and infectious foci. Progress has come from the development of effective preparations of the steroid hormones and diethylstilbestrol, and from the working out of the details of their application.

8 Cumberland Avenue

Discussion

Dr. Marion W. Westermeyer, Fairlee, Vermont: Is 1 international unit of progestin equivalent in effectiveness to 1 mg. of progesterone?

A Member: Would you give thyroid routinely in all cases of functional disorders, and how much do you use?

Dr. W. J. P. Dye, Wolfeboro: A great many women whom I have seen are unable to take stilbestrol by mouth because of gastrointestinal symptoms and even nausea and vomiting. What do you do in this type of case, and do you have the same difficulty?

Dr. Smith (closing): One international unit of progestin is equivalent to 1 mg. of progesterone. Progestin is effective, but the synthetic hormone is cheaper and more easily available.

In regard to thyroid extract, I give it almost routinely to patients with functional disorders, usually in doses of 1 gr. or less daily.

For those patients who suffer gastrointestinal disturbance from stilbestrol, I am now changing to estrone sulfate. It costs a good deal more, but so far I have found it worth while.

METHODS OF DIAGNOSIS OF JAUNDICE*

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A STUDY of the errors in diagnosis has already been reported[1] in 500 cases of jaundice that came under our observation on the Second and Fourth Medical Services at the Boston City Hospital during the last six years. In the present paper the clinical and laboratory methods that proved most useful in the diagnosis of these cases are reviewed. This series included most types of jaundice, such as complete and partial biliary obstruction, acute and subacute infectious and toxic hepatitis, the cirrhoses, — portal, biliary, pigmentary, toxic and cardiac, — fatty liver, tumors and syphilis of the liver, and hemolytic anemia.

On account of variation of symptoms, latent or exceptional cases, multiple diseases in a single patient and the large number of factors that go to make up the clinical picture, the number of possible combinations of symptoms and signs in any given disease causing jaundice is large, and 100 per cent accuracy of diagnosis can never be attained. The diagnosis may be laboriously built up from a collection of clues or may be obvious at once, as in arsphenamine hepatitis, prolonged painless complete obstruction and chronic low-grade familial hemolytic anemia.

HISTORY

The age incidence in four important groups is given in Table 1. In patients under thirty the cases of infectious hepatitis comprised 40 per cent, those of cholecystitis 15 per cent, and those of cirrhosis 9 per cent; there were no tumors. Infectious hepatitis may, however, occur at any age; 12 per cent of the cases occurred in patients over sixty, and the oldest of these, on whom an autopsy was performed, was eighty-seven. The large majority of cases of cirrhosis and cholecystitis occurred in middle life, and 80 per cent of the tumors were in patients over fifty. Painless jaundice in youth first suggests infectious hepatitis, and in patients over fifty cholecystitis, cirrhosis or tumor.

TABLE 1. *Age Incidence.*

DIAGNOSIS	NO. OF CASES	PERCENTAGES		
		UNDER 30	30–50	OVER 50
		%	%	%
Acute infectious hepatitis	101	40	32	27
Cholecystitis	71	15	31	53
Cirrhoses	161	9	40	51
Tumors of liver and bile passages	83	0	19	81

The family history sometimes strongly suggested hemolytic anemia, and sometimes gall-bladder disease or cancer.

The jaundice in the familial hemolytic cases was often slight and chronic — having been present for years. With incomplete obstruction by gallstones it was variable in duration and in degree, owing in part to the ball-valve action of stones in the common duct. In complete obstruction, which was due almost entirely to tumors, it was continuous and progressive over weeks or months until relieved by operation. In acute and chronic hepatitis the jaundice lasted for days, weeks or even months, depending on the degree of liver damage. Rarely a patient with hepatic cirrhosis remained continuously jaundiced for many months. Many patients were poor observers of the onset and variation of jaundice. (See also the paragraph on the depth of jaundice under "Laboratory Tests," below.)

Pain was important in its position, radiation, recurrence, character and relation to the onset of the jaundice. Acute and chronic hepatitis, stricture, hemolytic anemias and tumors are often described as causing so-called "painless jaundice." This is not strictly true. Pain occasionally occurred in acute and chronic hepatitis, and in rare cases was intense, with an extremely tender liver. Tumors often caused some pain, which was especially severe in the pancreas, but brief, sharp attacks of colic requiring morphine and recurring at intervals over weeks or months were much more frequent in cholecystitis and gallstones.

A history of exposure to liver poisons, such as arsenic, cinchophen, chloroform, carbon tetrachloride, gold thiosulfate and so forth, or to an infection at the onset of jaundice, was important.

Fever occurred in infection of the gall bladder, bile passages, liver or portal vein and in late cancer, and also in severe, acute hepatitis. If high and continued it was an extremely serious sign.

The distinction between acute liver disease and acute necrosis in chronic liver disease was sometimes difficult. A chronic portal or toxic cirrhosis may remain latent for so many months or years that the absence of previous symptoms cannot be relied on. Chronic disease was suggested if at the onset gross changes were found in the size, surface or density of the liver, all of which were out of proportion to the mild or moderate acute attack, or if such changes persisted long after the simple attack was over.

The course often aided diagnosis. A short course of moderate to severe jaundice (icteric index, 50 to 200) with marked loss of liver function was more frequently due to hepatocellular damage than to obstruction. The course may also be helpful in differentiating cancer from cirrhosis. If the disease is terminal, death naturally results in either disease;

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if it is not terminal, cirrhosis may improve and as a result cancer can be ruled out. Complete obstruction due to cancer almost never improves, but in one exceptional case with an enlarged, hard, irregular-shaped liver the jaundice improved greatly and the gray stools became brown; a cancer of the gall bladder had ulcerated into the colon and had thus relieved the obstruction of the common duct.

Gall-bladder disease proved to be probable in patients in middle life in whom an earlier diagnosis of acute hepatitis or incipient cirrhosis had been made. The Graham test was highly useful after the jaundice had disappeared and the liver function was normal or much improved.

Physical Examination

An enlarged liver was a valuable sign of hepatic disease but gave little help in deciding on its type. The liver was usually enlarged in hemolytic anemia, passive congestion, infectious or toxic hepatitis, cirrhosis, tumor, biliary obstruction, abscess, cholangitis, fatty liver and general infections. A distinctly small liver was found in only a few cases of acute necrosis — acute yellow atrophy — or atrophic portal cirrhosis. The density and irregularity of surface was of greater diagnostic value, but opinions were sometimes conflicting owing to the difficulty of feeling the liver through an abdominal wall that was thick, rigid or distended or contained irregular-formed deposits of fat. A granular, dense liver may be described as nodular, but in this series the term was reserved for livers with nodules or irregular-shaped deposits over 1 to 2 cm. in diameter, which were found only in tumors, the nodular hyperplasia of toxic cirrhosis and hepar lobatum. There was no case of tuberculosis of the liver.

Most of the firm livers resulted in a diagnosis of cirrhosis and all the stony-hard ones in a diagnosis of cancer. In passive congestion or fatty liver, a large, smooth organ of normal consistence presented no difficulties in diagnosis.

The smooth outline of an enlarged gall bladder was occasionally lost as a result of adhesions to the bowel, omentum, enlarged lymph nodes and so forth, and the organ resembled an enlarged liver. Tumors of the right upper quadrant of the kidney, adrenal glands, colon and so forth are rarely associated with jaundice.

A dilated gall bladder is said to be found in about half the cases of tumor involving the common duct (Courvoisier's law). In 33 cases of complete obstruction, after ruling out 1 case of cholecystitis, 2 with previous cholecystectomies and 1 in which the obstruction was above the cystic duct, there remained 29 cases of malignant obstruction of the common duct. The gall bladder was palpable on repeated examinations before operation in only 9 of these. A dilated gall bladder is important in diagnosis only if it is felt, and palpation may be difficult on account of ascites or distention. Complete absence of bile from the bowel, shown by urobilinogen tests or biliary drainage, was important evidence of tumor. If there were both a large, smooth, palpable, nontender gall bladder and signs of complete obstruction, the diagnosis of tumor was practically certain.

An enlarged spleen, ascites, abdominal varices and spider angiomas all pointed toward the medical types of jaundice — acute hepatitis, cirrhoses and so forth — rather than the surgical.

A palpable spleen had definite value in suggesting hepatitis rather than tumor. In the 27 proved cases of tumor of the liver the spleen was not felt in any, whereas it was felt in 10 (27 per cent) of the 38 proved cases of cirrhoses and in many cases of severe acute hepatitis. The roentgen ray sometimes showed an enlarged spleen that was not palpable, and it was sometimes found enlarged at autopsy although not palpable during life. In the 4 cases of cancer that were diagnosed as cirrhosis, the spleen was not palpable. It was enlarged in 7 of the 15 cases of hemolytic anemia of various types.

Ascites was found in both acute and chronic hepatitis and in cancer. In the latter, the specific gravity of the fluid was usually above 1.014 if the peritoneum was involved. It was absent in obstruction due to gallstones.

Spider angiomas of the skin (Eppinger,[2] Williams and Snell[3] and Patek et al.[4]) were found only in well-developed cirrhosis. They were the size of a nickel or dime and consisted of a group of fine arteries radiating from a common center. Pulsation was easily seen on pressure with a glass slide. The angiomas appeared only in the part of the body drained by the superior vena cava — that is, the face, neck, shoulders, chest and arms.

Biopsy of available lymph nodes was at times extremely useful.

Peritoneoscopy[5,18] is a valuable method of diagnosis that had only a limited use in this series. Its chief value in jaundice is the discovery of cancer or cirrhosis by vision or biopsy. The risk of biopsy is small when it is done with the electrocautery after using vitamin K. In a small number of cases the method fails because of adhesions.

The so-called "liver odor" (fetor hepaticus[2]), which is marked only in acute necrosis, had a vaguely suggestive value in diagnosis.

Laboratory Tests

Most liver-function tests were at their best in judging the degree of damage and surgical risk and in following progress rather than in aiding differential diagnosis, but with serial tests the course of changes of the liver function had some value in diagnosis; for example, in cancer it did not clear up, in complete obstruction it became worse, and in acute, toxic and infectious hepatitis and in cirrhoses — except in very severe cases or in the late stages — it improved.

The depth of jaundice judged by the icteric index gave little or no help in single cases in deciding between obstructive and acute hepatocellular jaundice. There was a wide range, and the averages were close. In 100 cases, the icteric index was as shown in Table 2. The jaundice was often slight and

TABLE 2. *Maximum Range and Averages of Icteric Index.*

DIAGNOSIS	NO. OF CASES	RANGE OF MAXIMUM	AVERAGE MAXIMUM
Acute hepatitis:			
Infectious	17	22–250	102
Toxic	17	50–200	118
Complete obstruction	31	65–200	116
Cirrhosis and partial obstruction	35	10–225	59
Total	100		

chronic in cases of familial hemolytic anemia. The qualitative van den Bergh test, by indirect and direct reaction, also helped to distinguish hemolytic jaundice from other types. This had only limited clinical value, as already explained. The tint of the jaundice — orange, greenish, bronze and so forth — had little value in distinguishing the obstructive from the hepatocellular type.

The test for urobilinogen in the urine had more diagnostic value than did other tests because it depends on the metabolism of the liver and also on the presence of bile in the bowel. Continued complete absence for two weeks or more strongly suggested complete obstruction of the bile ducts. The urobilinogen in the urine was almost always decidedly increased at some period in the course of acute hepatocellular disease. This test was unsatisfactory in the differentiation of partial obstruction — stone, stricture and cholangitis — and chronic cellular damage.

Bilirubin in the urine usually accompanied an increased icteric index in the blood in all types of jaundice except that due to hemolytic (acholuric) anemia. This absence of biliuria in well-marked icterus was suggestive, but was a minor factor in the diagnosis of hemolytic anemia compared with the blood examination and other clinical data. The history, anemia, icterus, splenomegaly, small spherocytes, increased fragility of the red cells, reticulocytes, lack of bilirubin in the urine (usually), excess of bile pigment in the feces, and an indirect van den Bergh reaction in the blood were distinctive. The presence of bile in the urine did not rule out hemolytic anemia, since in some cases there was combined liver damage. Abundant bilirubin in the urine was found in 5 of 14 cases in which hemolytic anemia was combined with cirrhosis, gallstones or passive congestion of the liver.

Many attempts to diagnose obstructive from hepatocellular jaundice have been made by the use of various determinations, such as the total blood cholesterol and cholesterol ester, the blood prothrombin levels and their response to vitamin K, galactose and glucose tolerance tests, hippuric acid excretion, serum phosphatase levels and cephalin flocculation tests.* There is a fundamental difficulty in this differential diagnosis; in hepatocellular damage — acute and chronic hepatitis — both metabolic and excretion tests are below normal, usually far below, whereas in pure external obstruction in the *early stages* the tests are normal or close to it, but in later stages of obstruction the lobular cells also become damaged and the tests closely resemble those of the hepatocellular group.

The total blood cholesterol was usually increased in obstructive jaundice. The prothrombin test proved an important measure of the bleeding tendency, and a low test that did not respond to vitamin K gave a bad prognosis, but the cholesterol ester levels and prothrombin tests† had only limited value in differential diagnosis. The sole diagnostic point noted in the prothrombin test was that the percentage was much more likely to rise rapidly to normal after treatment with vitamin K in obstructive jaundice and healing acute hepatitis than in chronic hepatitis (cirrhoses).

Other tests that are extremely sensitive, such as the bromsulfalein and hippuric acid excretion tests, were positive in all types of liver damage and had no differential value. The bromsulfalein test was used only when jaundice was slight or absent. Occasional high retention with a low icteric index was an important sign of liver damage without indicating the kind.

The presence of bile pigment in the stools is important in estimating biliary obstruction. No test was better than a rough estimate of color with the eye except the elaborate Watson test for urobilinogen; a simplified Sparkman[8] test also gave a rough estimate. The disappearance of urobilinogen from the urine was a useful guide to lack of bile pigment in the feces. A series of tests, done daily if desired, is far simpler than medical biliary drainage. A period with acholic stools often occurred in acute liver necrosis, but this rarely lasted more than a week — in exceptional cases two or three weeks.

Early tests for urinary diastase had great value in the diagnosis of acute pancreatitis as a cause of jaundice.

A change in the serum proteins, reduction of the serum albumin (normal about 4.5 gm. per 100 cc.) and lowering or reversal of the albumin-globulin ratio (normal about 2.0) were found in nearly all cases of well-marked disease of the liver and seemed to run parallel to the extent of liver damage. This change may be looked on as an index of liver failure and is highly valuable in the prognosis of chronic liver disease, as well shown by Post and Patek,[9] but has little or no value in single cases in diagnosing the type of disease — whether acute or

*The cephalin flocculation test[6] was used in only a small number of recent cases.

†Quick's[7] one-stage method for prothrombin was used.

chronic hepatitis, cancer of the liver or external obstruction. This is clearly shown in Table 3.

The range of the serum albumin and globulin levels and of the albumin-globulin ratio was similar in the four groups of cases, and the values in single cases apparently depended on the severity of the

TABLE 3. *Serum Protein Values in 50 Consecutive Cases.*

DIAGNOSIS	No. OF CASES	SERUM ALBUMIN gm./100 cc.	SERUM GLOBULIN gm./100 cc.	ALBUMIN-GLOBULIN RATIO	AVERAGE ALBUMIN-GLOBULIN RATIO
External obstruction (gallstone or cancer	11	1.5–5.2	1.9–2.7	0.3–1.3	1.0
Acute hepatitis ..	11	1.7–4.7	1.8–4.4	0.6–2.2	1.4
Cirrhosis	22	1.5–4.5	2.1–6.4	0.3–1.6	0.8
Carcinoma of liver	6	1.4–3.2	2.4–4.8	0.4–1.2	0.6
Total	50				

illness rather than on the type of disease. All the cancers of the liver were fatal, as were 20 of the 22 cirrhoses, 6 of the 11 external obstructions and 5 of the 11 cases of acute hepatitis.

A positive blood serologic reaction in jaundiced patients does not usually indicate syphilis of the liver. Hepatic cirrhosis and syphilis of the liver are often associated in the literature. In the present series, of 38 cases of cirrhosis with jaundice that came to autopsy there were 7 cases (18 per cent) with a positive Kahn or Hinton reaction but no evidence of syphilis of the liver. In 13,219 general autopsies at the Boston City Hospital between 1928 and 1937 there were 487 cases of cirrhosis of the liver and only 18 cases of acquired syphilis of the liver,* making the percentage of syphilis of the liver 3.7 per cent among the cirrhoses and only 0.14 per cent in the total group. McCrae's[10, 11] statement that syphilis of the liver should be considered in every case of hepatic disease in which the diagnosis is obscure probably applies to the pre-Wassermann days, chiefly covered by his figures, when only 1 case in 7 was recognized clinically. This is at present evidently a rare disease.

Since the only known case of syphilis of the liver in this series showed a negative Hinton reaction and all the other cases with positive Hinton reactions that came to autopsy or operation showed no syphilis of the liver, it cannot be said that the blood serologic test was of much help in this diagnosis. In the last ten to twenty years, most jaundice in syphilitic patients has been due to toxic hepatitis following the use of arsenic in treatment.

The roentgen-ray examination often detected disease of the gall bladder or the primary source of a cancer of the liver, and the discovery of early esophageal varices occasionally aided the diagnosis of cirrhosis before other signs were clear. The Graham test cannot be relied on during an attack of jaundice, when the liver function is usually low and the dye is poorly excreted; the test should if possible be made between attacks of jaundice. Biliary drainage was not extensively used on account of the time required, but it has special value when there is too much jaundice — and too poor liver function — for a Graham test.

No laboratory test was diagnostic without the clinical background. Improved diagnosis with the addition of laboratory tests was sometimes due not wholly to the tests but partly to more intense study of cases and added clinical experience. At the present time especially, tests with a simple technic easily available to the practitioner or small hospital have the preference. For a fuller discussion of liver-function tests and laboratory data, the reader should consult recent papers on this subject.[12–17]

The discovery of primary cancer of the liver, which develops chiefly in cirrhosis, is difficult by any method. The clinical pictures of late hepatic cirrhosis and primary cancer (hepatoma) are closely similar — namely, gastrointestinal symptoms, discomfort or pain in the right upper quadrant, weakness, loss of weight, hematemesis, fever, jaundice, ascites, anemia, enlarged liver, positive roentgen-ray examination and low liver function. There seems little or no possibility of succeeding in this differential diagnosis unless there is an external nodule or nodules in the liver that can be palpated or discovered on its surface by the roentgen ray or peritoneoscope, or unless there are metastases.

During the last six years we have seen 2 proved cases of primary cancer of the liver in patients with cirrhosis. In one, that of a man of sixty-four with jaundice, the evidence pointed equally to cirrhosis and to massive cancer of the liver from an unknown source, and both diagnoses were given equal value. In the other, that of a Chinese of sixty-six, a diagnosis of hepatic cirrhosis and cancer of the esophagus, with metastases to the lung, pleura, lymph nodes and bones, was made. At autopsy, cirrhosis, primary cancer of the liver, epidermoid cancer of the esophagus and a teratoma of the lung with adenocarcinoma were found.

SUMMARY AND CONCLUSIONS

The course of the jaundice often aids diagnosis, and since cases of jaundice are rarely emergencies, a short study period is useful. Tests of liver function should be repeated in series.

A short course of moderate to severe jaundice with marked loss of liver function was due oftener to hepatocellular damage than to obstruction. Acute deep jaundice with brown stools was almost always of the hepatocellular type.

The value of the depth of the jaundice, the size of the liver and a palpable gall bladder were often overestimated in differential diagnosis. The icteric index in acute hepatitis and complete external biliary obstruction were much alike. An enlarged liver was a valuable sign of hepatic disease, but was of such common occurrence that it gave little help in deciding the kind. The gall bladder could be

*All these syphilitic livers in adults showed more or less fibrosis and were classified as syphilitic cirrhosis.

palpated in only one third of the cases of malignant obstruction of the common duct; complete absence of bile from the stools was far more frequent and constituted important evidence of obstructive tumor. Complete obstruction due to cancer almost never improved.

The spleen was not palpable in any case with tumor of the liver, but was felt in 27 per cent of the cirrhotic cases. Spider angiomas were found only in portal cirrhosis. Fever and leukocytosis in late cancer sometimes simulated cholangitis and liver abscess. In deep jaundice an absence of bilirubin in the urine suggested hemolytic anemia, a diagnosis that was readily confirmed by other tests.

The test for urobilinogen in the urine often gave direct help in diagnosis of complete obstruction from hepatocellular damage and from partial obstruction. Other tests, such as hippuric acid and bromsulfalein excretion, were positive in all types of liver disease and had no differential value. Some tests that are useful in prognosis and for which differential value has also been claimed, such as the amount of cholesterol ester in the blood, the prothrombin level and its response to vitamin K and changes in the levels of serum proteins and in the albumin-globulin ratio, had little or no differential value.

In the diagnosis of acute pancreatitis with jaundice, early tests for diastase in the urine proved simple and highly valuable.

Positive Hinton, Kahn or Wassermann reactions in jaundiced patients usually did not indicate syphilis of the liver.

The roentgen ray often detected gall-bladder disease, the primary source of a cancer of the liver and esophageal varices. During deep jaundice the Graham test had little value on account of poor excretion of the dye by the liver.

I am indebted to Dr. Emmanuel Deutsch for many liver-function tests done in the Surgical Research Laboratory, Boston City Hospital.

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THE THERAPEUTIC VALUE OF TWO NEW SULFONAMIDE COMPOUNDS, SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE, IN EXPERIMENTAL TRICHINOSIS*

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DESPITE the wide and successful use of sulfonamide compounds in the treatment of bacterial infections, they have not been found to be particularly promising as therapeutic agents in diseases caused by animal parasites. It must be admitted, however, that present knowledge of the value of these drugs in the treatment of parasitic diseases has scarcely advanced beyond the experimental stage. It has been shown that sulfanilamide is a complete sterilizing agent against the malarial parasite *Plasmodium knowlesi* in rhesus monkeys, but it is not usually effective in human malaria due to *P. vivax*,[1] whereas both promin and sulfadiazine are definitely active against the three common species of human malaria.[2] Encouraging results have been obtained with sulfaguanidine used to combat coccidiosis in chicks,[3] lambs[4] and calves.[5] Critical tests with sulfanilamide derivatives against amebic infections have not been performed. Fairley,[6] however, noted that amebic ulcers heal during sulfaguanidine therapy, but that they relapse after cessation of treatment. Keil[7] observed no effect on the numbers of bancroftian microfilariae in the blood of 9 lepers treated with Prontosil. McCoy[8] found sulfanilamide to be entirely ineffective in the treatment of trichinosis in rats.

At the present time there is no specific treatment for trichinosis. Constant world-wide search has utterly failed to find an anthelmintic that will remove the adult worms from the intestinal tract or destroy the larvae in the blood stream and muscles.

The physical properties of two new sulfonamide compounds, succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine), are such that they suggest possible anthelmintic activity. Both are sparingly absorbed from the gastrointestinal tract, and a high concentration can be maintained in the diseased intestine without causing untoward toxic manifestations.[9, 10] They have extremely high bacteriostatic properties, their action being essentially limited to the local effect on the contents of the gastrointestinal canal.[11] It therefore seemed important to determine whether these drugs also had anthelmintic properties in trichinosis, especially against the intestinal stages of the parasite.

The tests with both drugs were similar. A single experiment was made for each drug in the following manner:

Five guinea pigs, each weighing approximately 260 gm., were forcibly fed approximately 3000 infective Trichinella larvae. Two days later, at which time the worms had approached sexual activity in the small intestine,[12] treatment of 3 of the animals was started. Food was withheld for fifteen hours prior to treatment, but was replaced again after the first administration of the drugs. Each of the 3 treated guinea pigs received by a stomach tube at 9 a.m., noon, 3 p.m. and 6 p.m., on two consecutive days, 0.5 gm. of one or the other of the drugs‡ suspended in 1 cc. of water. Three days after treatment was begun, or five days after the infective feeding, 1 of the untreated and 2 of the treated animals were sacrificed and their intestines examined for adult parasites. The remaining animals, 1 untreated and 1 treated, were sacrificed thirty days after receiving the infective larvae. Direct microscopic examinations for encapsulated trichinae were made on bits of masseter and diaphragm muscles pressed between two glass slides.

The dosage used was arbitrarily determined. Poth and Knotts[9] fed dogs 1 gm. of succinylsulfathiazole per kilogram of body weight daily in six divided doses for ninety-five days without the development of toxic manifestations. A marked lowering of the number of coliform bacteria occurred after twenty-four hours and persisted throughout the experiment. According to Poth and Ross[10] phthalylsulfathiazole has two to four times the bacteriostatic activity of succinylsulfathiazole. It is believed, therefore, that our dosage, approximately 8 gm. per kilogram a day for two consecutive days, was adequate to demonstrate any trichinicidal effect of these drugs.

The results obtained from both drugs were essentially the same. No deaths occurred among the untreated and treated animals. The untreated animals showed no signs of trichinosis. Loss of appetite, loss of weight and transient soft stools were characteristic developments among all the treated animals. These were believed to be toxic manifestations of the drugs.

Adult worms were equally numerous in the intestines of both untreated and treated animals. The worms were alive and normally active, and the females were gravid with living embryos. Both animals sacrificed thirty days after infection appeared equally parasitized with encapsulated trichinae. Thus, no evidence was obtained that either succinylsulfathiazole or phthalylsulfathiazole has any value in the treatment of trichinosis.

SUMMARY

The effect of two new sulfonamide compounds, succinylsulfathiazole and phthalylsulfathiazole, in the treatment of experimental trichinosis is described.

The experiment showed that neither succinylsulfathiazole nor phthalylsulfathiazole is of any value in the treatment of trichinosis.

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‡The compounds for this test were supplied by Sharp and Dohme, Incorporated, Philadelphia.

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MEDICAL PROGRESS

MALARIA IN MASSACHUSETTS

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MALARIA has been known to exist in Massachusetts from the earliest colonial times. Unfortunately, the malarial parasite and the transmission of malaria by mosquitoes were not discovered until the latter part of the nineteenth century. Consequently, it is difficult to determine the magnitude of the malaria problem in Massachusetts previous to that time, since many clinical entities were confused because of the lack of diagnostic refinements. There is, however, a certain amount of information concerning the prevalence of intermittent fever, ague, bilious fever, malignant fever, pond fever or mortal fever, as malaria was variously called in earlier times. Perhaps the completest early account of malaria in Massachusetts is to be found in the Boylston Prize Dissertations of 1836, in which Oliver Wendell Holmes[1] presented a paper entitled "Indigenous Intermittent Fever in New England." This paper was based on a review of the previous writings on the subject and personal communications from physicians.

From his search among the early writings on medical history in New England, Holmes concluded that intermittent fever existed in at least several places in New England but that the records of its existence in the literature were scanty and inaccurate. The second portion of his paper consists of replies to inquiries that he had sent to physicians throughout New England. This method of surveying the malaria situation was more fruitful, and Holmes gathered a large amount of disconnected information on the prevalence of intermittent fever in this region. In many cases, there can be no doubt that the disease concerned was malaria. In some accounts it is apparent that it was tertian malaria. Many of these outbreaks of intermittent fever were due to movements of population, concerned mainly with new construction, in particular dams, and the drainage of marshes.

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The first epidemic of malaria in Massachusetts took place at the close of the eighteenth century and existed in the western portions of both Massachusetts and Connecticut along the Housatonic River basin. The second epidemic appeared from 1828 to 1832 in Connecticut along the shore of Long Island Sound, and slowly moved in a northeasterly direction, eventually reaching western Massachusetts. No appreciable number of cases were reported in Massachusetts after 1836. The third epidemic began in New Haven about 1850 and remained within the vicinity of Long Island Sound for the ensuing fourteen years. In 1865, the disease began to spread northward, and it first appeared in Massachusetts in Springfield in 1870. During the ensuing nine years malaria spread in a northerly direction up the Housatonic and Connecticut rivers.

In 1880, Adams[2] made a survey of the malaria situation since 1836, by means of correspondence, personal observation and inquiry. By this means, the existence of malaria was ascertained in forty-eight cities and towns, and its absence in one hundred and sixty-three. There were no replies from one hundred and twenty-eight towns, but the author states that replies were received from almost every place of any size or importance.

In 1884, Chapin[3] wrote a paper entitled "The Origin and Progress of the Malarial Fever Now Prevalent in New England." He gave data on the occurrence of malaria in Massachusetts in 1881, 1882 and 1883. In 1881, malaria reappeared in the towns where it had appeared the previous year, with an increase in the number of cases and in mortality. Chapin remarks that the term "malaria" was beginning to replace the term "intermittent fever" in Massachusetts. In 1882, malarial diseases continued in the same towns, with an increase in deaths. In 1883, there was a general decrease in the number of cases, although nothing had been done in the way of sanitation to secure the result. Chapin judged

that the decrease in malaria was entirely dependent on natural causes.

In 1889, Cook[4] made a study of malaria in eastern Massachusetts. He concluded that prior to the previous four years malaria as an epidemic disease was unknown in eastern Massachusetts. The then prevailing epidemic was in reality a continuation of the epidemic of the seventies that had occurred in the western part of Massachusetts. Since the summer of 1885 at least twenty-two cities and towns in the counties of Middlesex, Norfolk and Worcester, not counting those where there had been sporadic cases, concluded that whereas typhoid fever and other diseases had possibly complicated the picture, malaria did exist in the various epidemics that had been described by the several writers. He decided that the origins of the various epidemics could be discovered only by a careful study of contemporary local history, with special reference to movements of population and modes of living. He contended that even without any appreciable influx of immigrants from countries in which malaria was prevalent, the southern states could at any time have furnished a sufficient quota of malaria carriers to start an

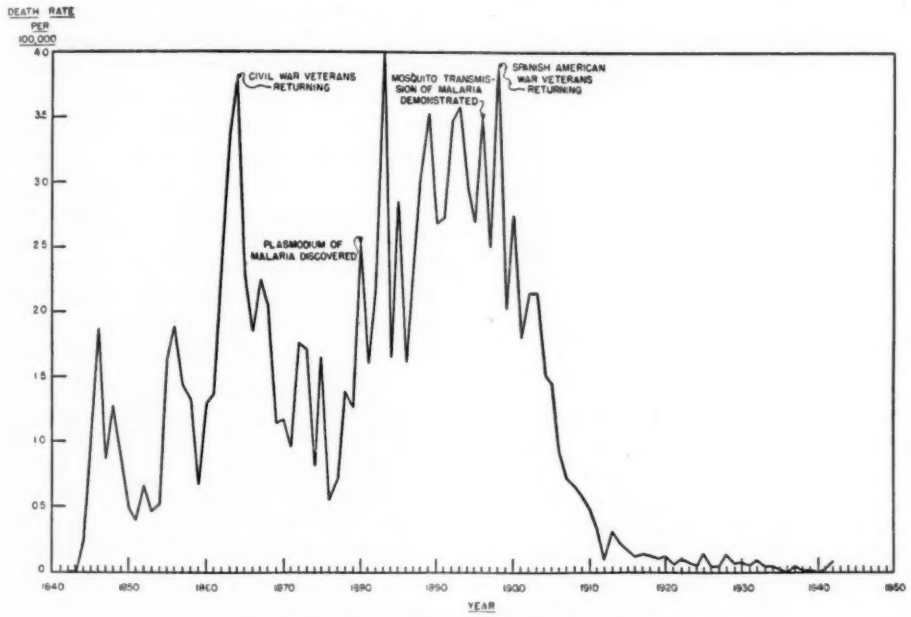

FIGURE 1. *Malarial Death Rate in Massachusetts.*

reported the prevalence of malaria. These towns were distributed along the Charles, Sudbury and Blackstone rivers.

In 1903, Smith[5] published in the *Boston Medical and Surgical Journal* a series of articles entitled "The Sources, Favoring Conditions and Prophylaxis of Malaria in Temperate Climates, with Special Reference to Massachusetts." Since the relation of mosquitoes to malaria as carriers was established by that time, and since the malarial parasite had been discovered, the diagnosis of malaria and the study of its spread are more reliable in the work of Smith than in that of the earlier writers mentioned. Smith made a survey of mosquitoes in Massachusetts and found *Anopheles maculipennis* — which was apparently confused with *Anoph. quadrimaculatus* — to be the commonest mosquito of any of the anophelines. He discussed the life, habits and breeding places of this mosquito, together with those conditions that favor mosquito breeding. Finally, he reviewed the history of malaria in Massachusetts and its status at the time in the light of the biological discoveries mentioned above. Smith epidemic under favorable local conditions. According to this author, the last invasion of New England by malaria, which began, roughly, in the sixth decade of the nineteenth century and extended through the first decade of the twentieth century, was largely due "to the great material development which found expression in many new public and private enterprises, such as the construction of railroad beds and highways, the introduction of public water supplies and sewerage plants, the building of mills and the drainage, filling and grading of suburban territory and the like." In connection with these enterprises, the sources of infection during the preceding thirty years he regarded as coming from the Italian, Hungarian and other immigrants from endemic foci and the contingent of Negro laborers from the southern states.

In 1926, Quinn[6] made a study of malaria in New England by mailing questionnaires to the health department of each of the New England states, to sixty-five representative cities and towns and to a number of hospitals. He pointed out that anophelines existed in all parts of New England below

a 2000-foot altitude, but that the mosquito is merely the connecting link between the malarial patient and the noninfected person. The plasmodium of malaria was brought in by immigrants from malarious sections of the world. Rigorous winters, cool summers and mosquito-control measures, however, together with quinine medication, prevented the completion of the necesssary chain of malarial patient, mosquito and noninfected person. The author reported the existence of an epidemic focus of malaria in Manchester, New Hampshire,

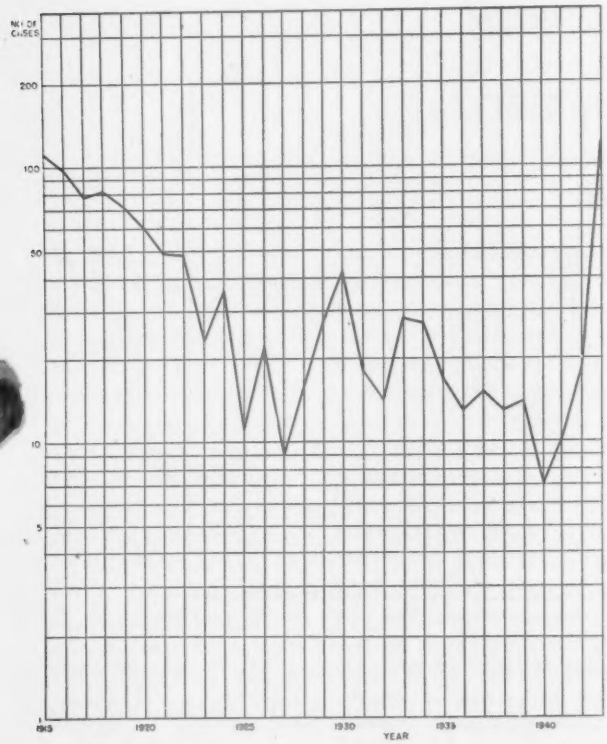

FIGURE 2. *Reported Cases of Malaria in Massachusetts.*

and in Connecticut, and also the incidence of malaria in several communities in Massachusetts, totaling 445 cases during the period 1917-1924.

Present Status of Malaria

Mortality statistics. Deaths from malaria were made reportable as early as 1842. At first these were reported as "intermittent fever" and "remittent fever"; from 1855 to 1900 the terminology was changed to "ague" and "remittent fever," and from 1901 to 1911 to "intermittent fever" and "malarial cachexia." Finally, since 1912 the disease has been reported as "malaria."

A study of these reported deaths (Fig. 1) reveals that there have been several peaks during the last hundred years. The first peak was reached in 1864 and was associated with an importation of the disease in Union soldiers who returned from the Civil War. A second increase in deaths due to malaria began to manifest itself in 1880 and continued until 1898, when the deaths again began to decrease. This second wave of deaths from malaria, as recorded in these reports, was caused by three factors. The first was the epidemic of malaria in Massachusetts that has already been discussed. The second was the effect of the Spanish-American War on this disease, which was seen in the peak of 1898; during this year many soldiers returned to Massachusetts after contracting the disease in Florida or Cuba. The third comprised better diagnostic facilities, in part due to the increased knowledge concerning malaria. The plasmodium was demonstrated during this period, and the mosquito transmission of malaria was proved, as well as the mosquito transmission of yellow fever.

With the turn of the twentieth century, deaths from malaria began to decrease rapidly, reaching a new low in the late 1920's. These deaths have averaged 1.8 per annum during the last ten years, indicating a case fatality of 8.9 per cent on a basis of the reported cases over the same period.

Morbidity statistics. It was not until 1914, however, that malaria itself was made reportable, when the Massachusetts Department of Public Health declared it to be a disease dangerous to the public health. At that time malaria was endemic in several places within Massachusetts.

In 1915, the first year for which the figures are complete, the reported incidence of malaria was the greatest. Since then the disease has a continued decreasing trend (Fig. 2) and reached an extremely low level in the five years immediately preceding the present war. Since 1941, however, there has been a continuous increase in the number of reported cases. Malaria was prevalent in Boston from 1915 to 1928. Most of these cases were in sailors who had acquired the infection in the tropics and were hospitalized in this city. Some of the cases, however, were connected with a new sewer project where Italian labor was employed. The high incidence of malaria in Chelsea from 1928 to 1935 is explained by the fact that the United States Marine Hospital was located there and received many sailors from foreign countries. The epidemic of 1918 in Ayer was due to the presence of large numbers of troops at Camp Devens some of whom were from the South.

In all there are three areas in Massachusetts where malaria has existed within the last twenty-five years. In each instance the disease ceased to be endemic in the area about twenty years ago, These areas are as follows:

The Charles River drainage area. The disease was prevalent here from 1915 to 1921. It apparently occurred first in Natick and Newton and spread to the neighboring communities of Dedham, Framingham and Wellesley. The town of Dedham has a large Italian colony. This is also true of Milford, in the upper part of the Charles River area, where malaria was prevalent from 1919 to 1924. Older residents of this part of the Charles River basin state that malaria was common in their childhood during the first

decade of the twentieth century. It is not unlikely that it may have been a hang-over from the epidemic wave of the last quarter of the nineteenth century. Probably there have been many more cases of malaria in this region than were reported.

The Blackstone River basin. Malaria was endemic in this region from 1915 to 1921, particularly in the towns of Uxbridge, Douglas and Northbridge.

The Taunton River basin. Here malaria persisted from 1915 to 1922. The same etiologic factors were responsible for disease in these regions as in the Charles River drainage area.

Malaria acquired in Massachusetts. The Massachusetts cases can be divided into two major groups, intrastate infections and out-of-state infections (Table 1). The former group represents but a small proportion of the total, less than 25 per cent of the reported cases being acquired within the boundaries of the Commonwealth. Moreover, most of these were cases induced in the treatment of syphilis of the central nervous system. Since 1930, a total of fourteen years, there have been only 11 cases that were probably naturally acquired within the Commonwealth. These patients were presumably bitten by Anopheles mosquitoes that were carriers of malaria. These cases were scattered throughout the Commonwealth (Table 2), and there is no evidence that there was any connection between them. In some cases — namely, the two children who acquired the infection during 1938 — there were malaria cases in the same or a neighboring household. The source of the infection in the other 9 cases, however, has not been established. Malaria is certainly not epidemic in this state, nor can it be said to be endemic. The number of naturally infected cases averages less than one a year, and the disease can therefore be called a rare phenomenon in Massachusetts. Doubtless, these infections were acquired from gametocyte carriers who infected the mosquitoes in the vicinity of the victim.

TABLE 1. *Reported Cases of Malaria in Massachusetts.*

TYPE	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	TOTALS
Intrastate:															
Natural	3	1	1	2	0	0	1	0	3	0	0	0	0	0	11
Therapeutic	5	5	2	12	5	1	2	3	2	5	0	6	1	0	49
Transfusion	0	0	0	0	2	0	1	0	0	1	0	2	0	0	6
Other	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Totals	9	6	3	14	7	1	4	3	5	6	0	8	1	0	67
Out-of-state:															
Civilian	13	6	2	12	10	13	8	9	7	5	5	1	2	3	96
United States Marine Hospital	20	5	6	2	6	2	0	1	0	0	0	1	0	0	43
Military	0	0	1	0	0	0	0	0	0	0	0	0	13	113	127
Totals	33	11	9	14	16	15	8	10	7	5	5	2	15	116	266
Miscellaneous	0	1	2	0	4	1	1	2	1	3	2*	0	2	5	24
Grand totals	42	18	14	28	27	17	13	15	13	14	7	10	18	121	357

*One congenital.

TABLE 2. *Cases of Natural Infection with Malaria in Massachusetts.*

YEAR	NAME	AGE	SEX	CITY OR TOWN
		yr.		
1930	M.B.	50	F	Uxbridge
	R.P.	38	F	Springfield
	M.W.	60	F	Newton
1931	W.R.	40	M	Boston
1932	C.W.	42	M	Athol
1933	H.O.	28	F	Westboro
	A.T.	23	M	Acton
1936	T.F.	50	F	Natick
1938	B.Z.	2/12	?	Worcester
	K.M.	2	M	Haverhill
	D.D.	19	F	Boston

During the last fourteen years, 6 patients have acquired malaria as a result of transfusions. To prevent a repetition of this unfortunate accident and the similar transference of syphilis, under a law[7] passed by the Massachusetts Legislature in 1938, the Department of Public Health made regulations relative to transfusions. On April 10, 1939, these regulations[8] became effective. The regulation reads, "No person shall introduce the blood, or any unsterilized fraction of the blood or tissue, of any donor into the body of any recipient unless said donor has never had syphilis or malaria and is free from any dangerous disease, so far as such freedom from past and present infection can be determined. . . ."

Of the cases of malaria reported in Massachusetts since 1930, over 75 per cent were acquired beyond the limits of the Commonwealth. During peacetime, these patients were civilians who had traveled in the southern United States or had visited tropical or subtropical countries. The largest group of out-of-state cases was reported by the United States Marine Hospital among merchant seamen who stopped at African ports. Since 1941, however, a new and important importation of cases has occurred. These are servicemen of the armed forces and prisoners of war. The vast majority of cases (95 per cent) reported in 1943 were from military organizations or among servicemen who were home on leave and developed symptoms of malaria after their arrival in the State.

Vectors of Malaria

During the summer of 1939, the Massachusetts Department of Public Health conducted, in cooperation with the Work Projects Administration, a survey of mosquitoes that were vectors of disease. This investigation was made on the recommendation of Brigadier General J. S. Simmons, then assistant surgeon of the First Service Command, United States Army, following an outbreak of equine encephalomyelitis involving about 300 horsse and

34 human beings.[9, 10] The survey determined the seasonal and geographical distribution of the fifty-six species of mosquitoes in Massachusetts, collected data on their life habits, and determined the epidemiologic importance of the various species. The conclusions reached were based on 49,084 collections comprising 278,557 specimens.[11] These mosquitoes and the accompanying data were gathered by one hundred WPA collectors and numerous volunteers enrolled with the co-operation of various federal and state institutions, local boards of health and other organizations.

Only two of the nine genera of biting mosquitoes of Massachusetts are known to contain species that may act as vectors of human disease. The statistical importance of these genera varies greatly (Table 3). Culex mosquitoes comprise 77 per cent of all mosquitoes and do not transmit any known disease of man in Massachusetts. Aedes represent 7 per cent of the mosquitoes, and of the twenty-one species in this genus, six have been shown to transmit the Eastern strain of equine encephalomyelitis in the laboratory.[11, 12] All the other genera except Anopheles comprise less than 5 per cent of the mosquitoes, and none of them are vectors of the disease. The genus Anopheles, comprising 12 per cent of the mosquitoes, is responsible for the transmission of malaria. In Massachusetts this genus is represented by five species, one of which, previous to the survey, was not known to inhabit Massachusetts (Table 4).

Anoph. quadrimaculatus is the most important vector of malaria in Massachusetts. It is an ubiquitous breeder but prefers large, clear bodies of water. Most numerous in July and August, it is a vicious biter and enters buildings oftener than any other mosquitoes except *Culex pipiens*, the common house mosquito, and *Mansonia perturbans*, which is most numerous in early summer. It has been collected in all parts of the Commonwealth and represents about one fourth of all Anopheles. Three other anophelines, *Anoph. maculipennis*, *Anoph. walkeri* and *Anoph. crucians*, transmit malaria and act as important vectors in other parts of the world. In Massachusetts all three of these are rare and epidemiologically unimportant in the transmission of malaria. *Anoph. punctipennis*, although a poor vector of malaria, because of its large numbers may play a role as a vector. It is distributed throughout the Commonwealth, is about three times as numerous as *Anoph. quadrimaculatus*, and breeds in almost any type of water collection, clear or foul, large or small.

From these observations, the possibility of an outbreak of malaria can be visualized. The vectors of malaria are present in all parts of Massachusetts. With susceptible persons likewise present, only one additional factor is needed to complete the cycle — namely, gametocyte carriers.

TABLE 3. *Genera of Massachusetts Mosquitoes, With Percentages of Adults and Larvae (1939).*

GENUS	ADULTS		LARVAE		No. OF SPECIMENS	RELATIVE INCIDENCE
	NO.	PERCENTAGE	NO.	PERCENTAGE		%
Aedes	8,409	46.4	9,733	53.6	18,142	6.6
Anopheles	1,260	3.8	31,728	96.2	32,988	11.9
Culex	7,443	3.5	206,206	96.5	213,649	77.3
Mansonia	6,663	91.1	649	8.9	7,312	2.6
Psorophora	4	44.4	5	55.6	9	0.0
Theobaldia	90	4.3	2,004	95.7	2,094	0.8
Uranotaenia	14	.6	2,312	99.4	2,326	0.8
Wyeomyia	9	36.0	16	64.0	25	0.0
Orthopodomyia	0	0.0	3	100.0	3	0.0
Totals	23,892	8.6	252,656	91.4	276,548	

TABLE 4. *Anopheles of Massachusetts, 1939.*

SPECIES	ADULTS		LARVAE		No. OF SPECIMENS	RELATIVE INCIDENCE
	NO.	PERCENTAGE	NO.	PERCENTAGE		%
crucians	0	0.0	20	100.0	20	0.1
maculipennis	30	21.6	109	78.4	139	0.4
punctipennis	302	1.5	20,442	98.5	20,744	62.9
quadrimaculatus	782	10.3	6,808	89.7	7,590	23.0
walkeri	78	49.7	79	50.3	157	0.5
Unidentified*	68	1.6	4,270	98.4	4,338	13.1
Totals	1260	3.8	31,728	96.2	32,988	

*Too small or too damaged for identification.

Epidemiology

From the study of malaria in the past and the present status of the disease in Massachusetts, it can be concluded that malaria has existed in this state as an endemic disease for many years in both the eastern and western portions, that it has crept over portions of the Commonwealth in at least three epidemic waves, that it has been practically eradicated from Massachusetts and that, at the present time, it is not a public-health problem. If the absence of malaria from Massachusetts could be depended on, there would be no justification for raising this problem at the present time.

Fortunately, climatic and environmental conditions in Massachusetts are unfavorable for the continued endemicity of malaria. Although there have been epidemic periods in the past, the disease has almost disappeared between these times of high prevalence. Each year, Massachusetts[13] becomes less favorable for the breeding of Anopheles mosquitoes. Ponds are kept clear of vegetation offering protection to the larvae; marshy areas about ponds and streams are gradually filled; and with the building of each new house more land is graded and more mosquito-breeding places are destroyed. These factors, limiting the breeding of vectors, and the excellent screening of houses and the prompt treatment of cases of malaria undoubtedly play important roles in preventing a major outbreak.

Malaria, however, increased to epidemic proportions following the Civil War and the Spanish-American War, when servicemen returned from malarious areas, bringing the infection with them. During World War I, although malaria was prevalent among the troops in southeastern Europe,[14] our forces did comparatively little fighting in areas of endemic malaria. Consequently, as Simmons[15] points out, there was only a slight increase of malaria in the United States Army and this was quite transient. In turn, there was practically no transmission of the disease from the military to the civilian population, and Massachusetts malaria rates were practically unaffected by the war of 1914–1918. Other parts of the world, however, were less fortunate. Malaria returned to plague areas in Europe, from which it had disappeared for years, and Russia experienced the most terrible epidemic of modern times.[14]

Malaria and the War

In the present war,[16] the importance of malaria cannot be minimized. The surrender of Bataan can be, at least in part, ascribed to malaria and the lack of quinine. Practically all the South Pacific islands are free from malaria except those between the Equator and latitude 20° S. from New Guinea east to longitude 170° E.[17] Malaya,[18] Burma,[19] India, Africa and the entire Mediterranean basin are rife with malaria.

The Army has taken all possible precautions to control malaria.[20] Under battle conditions,[21] however, exposure to malarious mosquitoes is inevitable, and consequently many soldiers, sailors and marines have acquired the parasites. Geiman[22] has reviewed the advances in research and their application to the malaria problems facing the entire world as a result of this war. On the return of these soldiers to the United States and to their homes or to hospitals, there is danger of spreading the disease to civilians. The danger of introducing malaria to Massachusetts,[23] to New York,[24] to other parts of the United States[25] and to Australia,[26] in fact to almost any region where anophelines are known to exist,[27] has been pointed out by numerous authors.

Through a program entitled "Malaria Control in War Areas," the United States Public Health Service [28] has been conducting a project designed to control breeding of disease-bearing Anopheles mosquitoes and to reduce potential malaria transmission in extracantonment zones of military establishments and in essential war industries. Up to 1943, the vast majority of this work was limited to the area south of the Mason and Dixon Line. Recently, as a result of surveys of mosquitoes made in the vicinity of certain military establishments in Massachusetts, the program has extended its activity into New England.[29] This organization[30] is giving special attention to areas adjacent to Army general hospitals where casualties from malarious areas may be quartered. Some of these hospitals are assisted by active control measures, others are undergoing entomologic surveillance, and in some, surveys have been completed. Similarly, prisoner-of-war camps are being surveyed and in some instances assisted with malaria-control programs. Thus far, only entomologic surveys have been made in and about military establishments in Massachusetts. In several instances, however, control measures have been instituted in military establishments against mosquitoes primarily as pests.

The Massachusetts Department of Public Health and the Reclamation Board[31] have been co-operating with the armed forces and with the control program of the United States Public Health Service described above in making surveys of the extracantonment areas of military establishments in this state. Thus far, the expenditure of money for mosquito control in Massachusetts has been directed at the nuisance and pest angle and not specifically against vectors of disease. As yet, in Massachusetts, no funds have been expended specifically against the anophelines. Data, however, are being assembled to enable efficient control measures against anophelines as soon as a need for these develop. In one instance the personnel of the Massachusetts Reclamation Board have been active in instructing a large number of troops in mosquito-control measures so that they in turn may become proficient in applying these measures against Anopheles when they go abroad into zones where malaria is prevalent.

The reintroduction of malaria into Massachusetts may come from three sources. The first of these is the presence of carriers of the usual strains in large numbers, thereby giving rise to cases in the immediate vicinity. If patients are properly treated and are kept under screens, especially after dusk, this danger can be reduced to a minimum, especially when combined with measures designed to reduce the anophelines below the level necessary for endemicity. Any such outbreak will be temporary and limited in geographical area, since the factors that are responsible for the eradication of malaria are still in operation and will again eradicate the disease. The second source is new species of mosquitoes that are better

vectors, which may be brought by airplanes and ships and thereby enhance the spread of the disease. The classic illustration is the introduction of *Anoph. gambia* from Africa to Brazil and the subsequent epidemic of malaria.[32, 33] More recently, *Anoph. albimanus* was discovered in an area adjacent to a Florida airport[28]; since this species is not native to Florida, there is only one explanation for its presence near the airport. Active disinsectization of all airplanes and ships from malarious areas is the only sure safeguard against bringing new vectors into Massachusetts. The third source comprises new species or strains of malarial parasites introduced either by human carriers or by mosquito vectors. Such a plasmodium, if it finds a more efficient vector, may create a serious outbreak.

Malaria Control

Adequate control of malaria must be based on one or more of the following procedures: control of mosquito vectors; protection from the bites of infected mosquitoes; immunization of susceptible persons; removal of sources of infection of mosquito vectors by isolation of cases or treatment of carriers; and prevention of entry of mosquito vectors and possible sources of infection into areas as yet unaffected by the disease.

Mosquito control. Certain conditions are necessary before a mosquito-borne disease can become epidemic or reach a high endemic index. One of these conditions is the existence of a numerical relation between the hosts, vectors and susceptible persons. When this relation is upset by a reduction of the number of vectors, the disease ceases to be epidemic and rapidly declines, either arithmetically or geometrically, depending on the interrelation of many factors. It becomes apparent that a moderate reduction in the number of mosquitoes below the critical level will markedly reduce the prevalence of the disease in an area where there are many immune persons, but in a region with many susceptible persons the reduction below the critical level must be much greater. This concept was developed by Ross,[34] who applied it to malaria. Carter[35] and Gorgas[36] applied it to yellow fever.

The bionomics of mosquitoes[37] are such that control measures must be designed to eliminate or control the larvae or the adults. The measures that are most effective in any area depend on the local factors and on the species of mosquitoes concerned. It is impractical and uneconomical to attempt to control all mosquitoes. The control measures must be directed against the species that it is desired to reduce below the critical level. Therefore, in order to ensure effective control measures, it is important to understand the bionomics, breeding habits, seasonal and geographical distribution and identification[38] of the species that are concerned with the transmission of the disease. Since local circumstances vary, it is necessary that a mosquito survey[39] be made before control measures are introduced into a new area for the purpose of controlling mosquito-borne disease. Even in controlling mosquitoes as a nuisance, it is necessary to determine their bionomics before an economical and efficient nuisance control can be expected.

Protection from mosquitoes. Effective protection from the bites of mosquitoes can be accomplished only under extremely limited conditions, especially in combat.[40] Screening and avoidance of unnecessary exposure are the most effective methods. Spraying in houses, and out-of-doors, the application of mosquito repellents and the killing of adult mosquitoes are adjuvants. For this method to be completely effective, man would necessarily have to remain behind screens at all times. Since this is a practical impossibility,[41] protection against mosquito bites is only partial.

Immunization of susceptible persons. There is no specific immunization against malaria. The suppressive treatment with quinine or atabrin is an attempt to destroy or suppress the multiplication of the plasmodium as soon as it is introduced into the blood stream. These drugs merely act as suppressives and not as prophylactics, and are not recommended for residents in Massachusetts. Atabrin[42] is about as effective as quinine[43] in preventing clinical attacks of the disease, and both drugs[44] are being used in combat areas. Plasmoquin[45] has not proved valuable as a suppressive and is not recommended for prophylactic use. The development of a good prophylactic against malaria would be one of medicine's greatest gifts to humanity.

Removal of human sources of infection. Removal of human sources of infection is effective only to a limited extent. Patients with the disease or gametocyte carriers, with the infecting agent in the circulatory blood, may act as foci of infection for vectors, and are usually the foci of outbreaks of the disease in new areas. It is therefore sound preventive medicine to isolate these persons in mosquito-proof quarters.

Prevention of entry into new areas. Malarial patients entering the country from abroad should be maintained under observation at least three weeks after the stopping of suppressive treatment with atabrin or quinine, since most cases develop symptoms by that time. The patients should receive adequate therapy in screened quarters,[42] and after discharge from the hospital must be followed up in order to detect recurrences adequately. In this way, most of these patients will be rendered noninfectious to mosquitoes and will not act as foci of local outbreaks.

Airplanes must be adequately treated to prevent the importation of infected mosquitoes. With the increase of speed of travel, many planes may transport patients from one continent to another within the incubation period of disease. New quarantine regulations and procedures to protect the Nation

from malaria and other infectious disease must be developed and implemented in the near future.

Conclusion

Three factors are necessary for the continued existence of malaria in any area.[46] These are gametocyte carriers, which are entering Massachusetts in increasingly larger numbers, chiefly as servicemen and prisoners of war; certain species of Anopheles mosquitoes that can transmit the disease; and susceptible persons who can be infected.

The prevention of malaria in the future and its control in Massachusetts can be achieved by two methods. The first is the prevention of the infection of Massachusetts mosquitoes by gametocyte carriers who may act as the source of the epidemic, through adequate treatment and screening of patients. This method, however, is not entirely dependable, since it is impossible to ascertain which asymptomatic persons are gametocyte carriers, and tests that could determine the presence of gametocytes in the blood of all persons who enter the Commonwealth are both difficult to perform and enforce.

The second and most practical method of controlling malaria is by an attack on the mosquito vectors. Such an attack, however, must be based on accurate knowledge of the distribution of the vectors. The recording of data on the seasonal prevalence and geographic distribution of the mosquito vectors of malaria is one of the accomplishments of the mosquito survey,[47] conducted by the Massachusetts Department of Public Health in 1939. The United States Public Health Service,[27] assisted by state and military agencies, is making detailed surveys of extracantonment areas of military establishments where malaria patients are likely to be hospitalized.

Should there be any evidence of spread, mosquito-control measures must be directed against those mosquitoes that are carriers of disease, the number of vectors thus being lowered to a number that is insufficient either to maintain the existence of malaria or to permit its introduction.

It is unlikely that malaria will again become endemic in Massachusetts as a result of this war. Sporadic cases may occur, but any larger outbreak will probably be short-lived and geographically limited. Under proper safeguards, Massachusetts and most of New England are relatively safe from any extensive epidemic of malaria.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30121

PRESENTATION OF CASE

A forty-seven-year-old housewife entered the hospital because of pain in the lower back.

The patient had been in apparent good health until one year prior to entry, when, following a cold, she developed a burning pain over the sacrum and lower back. Similar attacks recurred and apparently progressed in severity. Recently the attacks had lasted for three or four days and had forced her to remain in bed. She felt that she was never free of pain, although it rarely kept her awake. During acute attacks, hot packs and aspirin gave relief. About eight months before admission she noticed that the pain radiated to both legs. This was brought on chiefly by sitting for some time and then trying to stand up. She was unable to lift her legs, and attempts to move the thighs brought sharp shooting muscle pains, radiating from hip to knee. At the same time she noted a dull aching pain in the thigh muscles at intervals of about a month, which lasted three to five days. About one month before admission she developed a feeling of fullness and pressing down in the rectum, which was especially noticeable after sitting for some time. Bowel movements did not relieve the sensation. She had had a three-day episode of watery diarrhea with a small amount of blood. She had had night sweats for one year, which were said to be due to the onset of the menopause.

Nine years before entry it was discovered that the patient's serum gave a positive serologic test for syphilis; the spinal fluid was negative. She received antisyphilitic treatment for several weeks at that time, and a full course of treatment seven years later. One year before admission she had a left radical mastectomy for scirrhous carcinoma with axillary metastases, which was followed by x-ray treatment.

Physical examination showed a well-developed, fairly well-nourished woman in no distress. The incision over the left breast was well healed, and no evidence of recurrence could be found. The lungs were negative except for a few moist rales at the left base. The heart was normal. The abdomen was protuberant. There was increased lumbar lordosis. The posterior superior iliac spines were above the anterior superior iliac spines. Examination on standing showed full spinal motion; on flexion and extension from a flexed position, considerable pain was present about the sacrum. There was joint tenderness over the coccyx, over the sacroiliac joints posteriorly and along the attachments of the erector spinae muscles to the sacrum. In the sitting position passive movement of the spine was normal. Straight leg raising was 60° bilaterally, with stretching of the hamstrings. Rectal examination showed tenderness over the coccyx. Neurologic examination was negative.

The blood pressure was 140 systolic, 100 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 7700. The hemoglobin was 75 per cent. The urine was negative. Blood Hinton and Wassermann tests were negative. The blood sedimentation rate was 5 mm. in fifteen minutes, 38 mm. in thirty minutes, 49 mm. in forty-five minutes and 51 mm. in sixty minutes. A blood calcium was 11.1 mg. per 100 cc., the phosphate 4.7 mg., and the alkaline phosphatase 8.8 Bodansky units. Two lumbar punctures gave clear fluid with total protein of 53 mg. per 100 cc., a gold-sol curve of 0010000000 and a negative Wassermann reaction.

X-ray examination of the chest showed some scarring in the right upper lung field but was otherwise negative. The heart and mediastinum were slightly displaced to the right. Plain and special films of the lower spine revealed an area of rarefaction in the upper margin of the right sacroiliac joint that was surrounded by dense bone (Fig. 1). There was no evidence of disease in the lumbar vertebras or pelvis. A barium enema was negative.

The aches and pains in the thighs continued. There was considerable weakness. On the fourteenth hospital day the patient developed a slight sore throat and a feeling of exhaustion. The temperature was 102°F. Rales were heard in the left base, with increased bronchophony. The white-cell count was 21,300. Throat culture yielded a beta-hemolytic streptococcus. She was given intravenous fluids and recovered completely from this infection.

On the thirty-fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. THOMAS J. ANGLEM: May I see the x-ray films?

DR. LAURENCE L. ROBBINS: This is the rather sharply circumscribed area of rarefaction with dense margins that was described. Other than that I do not believe there is anything definite. These areas of calcification are within the abdomen. About the only thing that is at all suspicious is some questionable decalcification in the sacral region.

*On leave of absence.

DR. ANGLEM: Can you tell me more about the nature of the radiating pain that extended down the thighs? Was it sciatic in distribution?

DR. JOHN REIDY: At times she did have a radiating sciatic pain. In the examinations before admission to the hospital the pain had been of that description, but it subsided, particularly after rest in the hospital.

DR. ANGLEM: We have as the essential features of this case a history of pain in the lower back and sacrum of one year's duration, with the development four months later of a radicular type of pain radiating into the lower extremities. The pain appears to have been continuous, with recurring superimposed acute exacerbations of acute pain. Severe shooting pains were induced by lifting the legs. One month before admission the patient developed a feeling of pressure referred to the rectum that was not relieved by evacuation. She had one episode of diarrhea with blood in the stools, which lasted for three days. She had had night sweats for one year, which were ascribed to the menopause but may have arisen on some other basis.

After admission the patient developed a respiratory infection associated with weakness and exhaustion. This is described as a slight sore throat, but the constitutional symptoms seemed to have been severer than those one would expect from a slight sore throat. From this she appears to have made a good recovery.

The whole picture is complicated by the fact that the patient is known to have had syphilis in the past, carcinoma of the breast one year before, and x-ray evidence of old pulmonary tuberculosis.

The findings of possible significance are pain referred to the sacral and lower lumbar areas on motion and tenderness on palpation of the sacrum, the coccyx and the regions of the insertion of the erector spinae muscles. Also of considerable significance in a negative way is the absence of neurologic signs. The increased sedimentation time and the slight increase in alkaline phosphatase may be of significance, but they are not diagnostic. The increased spinal-fluid protein I believe to be of considerable significance. The x-ray findings may be independent of or related to the patient's present illness.

The symptom complex that this patient presents — pain in the lower back associated with radiation of pain of the radicular type into the lower extremities — is characteristic of a space-occupying lesion in the spinal canal involving the lower spinal nerve roots. Such a space-occupying lesion may arise from a variety of causes. Syphilis should be mentioned because of the patient's past history. It is, however, an uncommon cause of this type of

FIGURE 1. *Roentgenogram Showing the Area of Rarefaction in the Right Ilium.*

pain, and since the recent blood and spinal-fluid Wassermann reactions were negative, I believe we can disregard it.

Is there a chest film? The description of the film in the history suggests healed tuberculosis.

DR. ROBBINS: There is evidence of old tuberculosis.

DR. ANGLEM: But no sign of activity?

DR. ROBBINS: Nothing I can be sure of.

DR. ANGLEM: Tuberculosis may produce symptoms of this type when there is tuberculous involvement of the lower lumbar vertebral bodies with extension of tuberculous granulation tissue into the region of the spinal roots. There is, however, no evidence of such involvement in the lumbar vertebras to support this diagnosis.

The symptoms that this patient presented frequently arise on the basis of a protruded intervertebral disk. The story is characteristic except in certain minor respects — the absence of paresthesia and of any disturbance of the reflexes, which, however, are not essential for that diagnosis.

The onset is said to have followed a "cold." This cold may have been a nasopharyngitis, which is a not uncommon primary focus from which osteomyelitis develops. A low-grade osteomyelitis of the lumbar vertebras could produce the symptoms of which this patient complained, through formation of an abscess extending into the epidural space. The x-ray films, however, show no evidence of such a disturbance of the lumbar vertebras.

I find it difficult to relate the area shown by x-ray in the region of the right sacroiliac joint to this patient's symptoms. It does not have the usual features of metastatic cancer, and in view of its unilateral position and its circumscribed character, I do not believe that it is possible to account for the patient's bilateral symptoms on this basis. I believe we can safely disregard it.

A primary or metastatic tumor involving the cauda equina must be considered. Against a primary tumor are the relatively slow progress of the disease and the complete absence of definite neurologic signs after the duration of a full year. The same argument may be offered against a diagnosis of metastatic tumor. If she had had metastatic disease involving the cauda equina, originating from the breast carcinoma, I should expect it to have progressed more than it had in the course of a year and to have shown evidence of bone destruction by that time. Considering these various possibilities it seems to me that the basis of this patient's complaint was independent of the other diseases of which we have previous knowledge; hence, I believe that she probably had a protruded intervertebral disk.

DR. BENJAMIN CASTLEMAN: Would you like to express an opinion, Dr. Smith-Petersen?

DR. MARIUS N. SMITH-PETERSEN: I know the diagnosis. I, too, belittled the presence of the area in the posterior iliac crest. I thought that the changes seen in the x-ray film were due to surface changes, which often give an area of increased density surrounding an area of decreased density, but I was willing that the biopsy should be performed.

DR. PAUL ZAMECNIK: When axillary metastases are found, what are the statistics on finding further metastases? I have an impression that they are rather high.

DR. CASTLEMAN: The prognosis is poor in 75 per cent of the cases.

DR. ANGLEM: I considered another possibility, osteoid osteoma, based on the description and the appearance of the lesion in the sacroiliac area, but I did not see how the other symptoms could be explained on that basis.

DR. CARROLL B. LARSON: We explored the sacroiliac region for the lesion that was seen by x-ray, and we came down on an absolutely circumscribed area, as shown in the x-ray. A cross section of this area revealed a cellular-appearing homogeneous pinkish-gray material. I could make nothing out of it grossly. We excised the lesion entirely, and in so doing we uncovered a portion of the sacral side of the sacroiliac joint, including the cartilage. The trabeculation in the anterior body of the sacrum appeared abnormal. I cannot tell why, but it just did not look right, so I scooped out some of the material, which was very friable, and sent it as a separate and distinct specimen from the lesion in the ilium.

CLINICAL DIAGNOSIS

Osteochondroma of ilium.

DR. ANGLEM'S DIAGNOSIS

Protruded intervertebral disk.

ANATOMICAL DIAGNOSES

Metastatic carcinoma of sacroiliac region.
Fibrous dysplasia of ilium.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The microscopic examination of the material scooped out of the sacrum showed metastatic carcinoma. The well-circumscribed lesion in the ilium proved to be an area of fibrous dysplasia completely surrounded by metastatic cancer, but there was no carcinoma within the cyst-like area. The cancer, therefore, was not seen on the x-ray film.

CASE 30122

PRESENTATION OF CASE

A sixty-nine-year-old woman was admitted to the hospital for study.

The patient was rather confused and unable to give an accurate history. She had had rheumatic

fever as a child. Thirteen years before entry she had an episode of jaundice relieved by the removal of the gall bladder, which was said to have contained stones. Five years prior to entry, she had pain in the right flank radiating to the groin, nocturia, urgency, frequency, dysuria and pyuria. These continued off and on, and she was told that she had gravel in the urine. Two or three years before admission she was found to have an enlarged spleen and anemia; she subsequently had frequent attacks of anorexia, nausea without vomiting, gas and abdominal discomfort. One and a half years before admission, following an automobile accident, she developed intermittent attacks of dizziness, vertigo, tinnitus, headache, diplopia, soreness of the neck and tremors. One year before entry she had epistaxis on several occasions, but had had none since. During the eight months preceding admission she had had frequent loose, dark, watery stools, which had recently become normal following the use of Peptobismol. She had had ankle edema and dyspnea on exertion for several years, but these had increased in severity during the last few months before entry, and she developed occasional precordial pain on exertion. During this period she had considerable pain and stiffness in the back, right leg and both arms, and occasionally in the chest. She had lost about 40 pounds of weight over a period of years.

She had had several admissions to the Massachusetts Eye and Ear Infirmary for sinus trouble, bilateral cataracts and other eye troubles.

Physical examination showed a well-developed, rather obese woman in no distress. There was no enlargement of the lymph nodes. She was edentulous. The tongue was smooth. The left half of the diaphragm was elevated. The lungs were clear. The left border of cardiac dullness was 12.5 cm. from the midline in the fifth space. The sounds were regular except for occasional extrasystoles. A loud harsh systolic murmur was heard at both the apex and the base, but chiefly in the aortic area. A mitral diastolic murmur was also heard by one observer. The aortic second sound was greater than the pulmonic. The abdomen was protuberant and diffusely tender. A large mass was present in the region of the spleen, extending anteriorly to the midline and five fingerbreadths below the costal margin. The mass was smooth, movable, ballotable and tender, and moved with respirations. There was some tenderness in the left costovertebral angle. Pitting edema of the ankles and sacrum was present. Neurologic examination was normal except for diminished vibration sense in the left leg and absent ankle jerks.

The blood pressure was 146 systolic, 90 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 3,680,000, with 64 per cent hemoglobin. The white-cell count was 2200, with 64 per cent neutrophils, 32 per cent lymphocytes and 4 per cent monocytes. The platelets were diminished in number, and the red cells were hypochromic. The urine was cloudy, with a pH of 7.5 and a specific gravity of 1.012. There was a + test for albumin, and 1 or 2 red cells per high-power field in the sediment. The stools were guaiac negative. The nonprotein nitrogen was 10 mg. per 100 cc., the blood calcium 10.1 mg., and the phosphorus 1.6 mg. The phosphatase was 4.1 Bodansky units. A blood Hinton test was negative. The blood protein was 6.6 gm. per 100 cc., the albumin being 3.4 gm. and the globulin 3.2 gm. The van den Bergh test was normal.

X-ray examination showed the heart to be enlarged to the left. There was some fullness in the region of the left auricle. The lung roots and fields were not unusual. A large mass was seen in the left abdomen; this was separated from the kidney but not distinguishable from the spleen. The left kidney was somewhat larger than usual. There was an opacity in the right upper quadrant the nature of which could not be determined. There were hypertrophic changes in the spine.

X-ray films of the skull were not remarkable. A barium enema revealed normal filling of the colon. The splenic flexure was displaced anteriorly by an enlarged spleen. A gastrointestinal series was negative except for several longitudinal varices in the lower esophagus. An intravenous pyelogram was somewhat unsatisfactory because of the previous barium. No definite stones could be seen, and except for a slightly low position of the left kidney, no evidence of disease of the urinary tract was observed.

After the first day or two, the patient complained of pain and burning on urination. The urine was found to contain innumerable white cells. A culture gave many colonies of colon bacilli. On the eighth day she was given 4.5 gm. of sulfadiazine, followed by 2 gm. daily for the next three days, at the end of which time the urine had cleared up considerably. The white-cell count was 1800, with 65 per cent polymorphonuclears, 27 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The platelets were still decreased in number. The hemoglobin was 7.5 gm. per 100 cc. On the fifteenth day a cephalin flocculation test was ++++ in twenty-four hours and ++++ in forty-eight hours. The prothrombin time was 28 seconds (normal, 18 seconds). The hematocrit was 34 per cent. There was 60 per cent retention of bromsulfalein at the end of forty-five minutes.

The patient was given intramuscular injections of liver extract, 15 units daily. On the eighteenth day she had a severe shaking chill with a fever of 101°F. In the next two days she had colicky pain in the right costovertebral angle and flank. She was nauseated but did not vomit. Examination

showed extreme tenderness in the right-costovertebral angle and flank. One urine examination gave a ++ test for albumin, with a specific gravity of 1.010 and innumerable red cells. An examination on the following day showed large numbers of white cells.

On the twenty-first day the patient had a chill with elevation of temperature to 106.4°F. A blood culture yielded colon bacilli in both flasks. The white-cell count was 1500, and the red-cell count 3,190,000 with 7.5 gm. of hemoglobin. She was given a transfusion of 500 cc. of blood, followed by sulfadiazine for the next two days. The temperature remained elevated, and the pulse became irregular, rapid and of poor quality. There were basal rales. She was given 4 cc. of Cedilanid intravenously, and intravenous saline in glucose and sodium sulfadiazine, but died on the twenty-third hospital day.

Differential Diagnosis

Dr. Chester M. Jones: One of the things that impresses me is that more and more at these conferences we are getting patients farther along in life, thus increasing the necessity for a multiplicity of diagnoses. Many different things happened to this woman that ought to be remembered in the subsequent events. She had had rheumatic fever, jaundice, gallstones, renal colic, an enlarged spleen and anemia. There is also a good description of the symptoms of a subdural hematoma. One year before entry she had epistaxis on several occasions, which is just one more item that adds to the confusion of the story. She had had loose stools, which possibly were tarry, and finally, symptoms of pericardial pain, exertional dyspnea and pain in the extremities and chest. The cataracts and other eye troubles are further evidence of degenerative disease.

It seems to me that with this clinical story it is simply a question of adding up the facts and presenting them as probabilities. I do not see any reason for assuming that there was some rare condition. She had had rheumatic fever and presented the physical signs that are consistent with old, healed mitral stenosis. She is said to have had a mid-diastolic murmur, which is characteristic of this condition.

Dr. Paul D. White: What about the aortic valve?

Dr. Jones: She could have an old rheumatic involvement of the aortic valve as well. There is no story of a thrill, transmission of that murmur or a wide pulse pressure.

According to her testimony she had gallstones, which gallstones were removed, and she had jaundice in one of the attacks preceding operation. At entry, the x-ray studies are said to have shown a homogeneous mass in the right upper quadrant whose nature could not be determined. I cannot do any better than to guess that that might conceivably have been a gallstone that was still in the common duct. The most that I can say is that she had had gall bladder disease in the past — gallstones and jaundice — and had the makings of chronic intrahepatic disease because of the persisting attacks.

There is a perfectly good story of renal stones, and there is no reason to think that the patient did not have them. She had pain in the right flank radiating to the groin, nocturia, frequency, urgency and pyuria. There was evidence of urinary-tract disease during her stay in the hospital, in that she had pain and tenderness in the right costovertebral angle, right pleural pain, a shaking chill, and urine that contained on one occasion red cells and on another pus. There were colon bacilli in the urine, and it is not unreasonable to think she had a urinary-tract infection arising from gravel or stone in the right kidney, which could logically explain the signs and symptoms she showed in the hospital. Whether the hematuria was due to an intrarenal tumor is a matter of pure speculation.

She was said to have had an enlarged spleen and anemia three years before she came in, and I see no reason to doubt that — in other words, she may have had so-called "Banti's disease" as a result of thrombosis of the splenic vein. There is, however, no episode to suggest such a diagnosis. The finding of Banti's disease in a person of her age is unusual. Therefore, it seems to me wiser to admit that she had something more than involvement of the splenic vein, in which case one wonders about intrahepatic disease — cirrhosis of the liver with splenic enlargement. We know that she had esophageal varices by x-ray and also leukopenia, findings that go with any chronic serious intrahepatic lesion even when the disease is relatively quiescent. A splenic tumor fits in with chronic liver disease, and varices can be associated with portal hypertension rather than with thrombosis of the splenic vein. On the basis of the laboratory findings we know that there was a serious intrahepatic complication: the cephalin flocculation test was ++++, there was marked dye retention and the prothrombin time was increased.

The attack of dizziness and vertigo, a year and a half before admission, following the automobile accident, makes me wonder if she had concussion and a subdural hematoma. At any rate these symptoms date from the accident. The nosebleeds may have been due to focal venous engorgement or she may have had marked hypertension, which she did not have on arrival at the hospital. One would have to guess rather than state that she had hypertension. The dark watery stools I cannot explain, unless one wants to say that she was bleeding from esophageal varices.

The patient had precordial pain on exertion, ankle edema, dyspnea and shortness of breath, and it seems

reasonable to suppose that they were cardiac in origin. She was sixty-nine years old when she developed the symptoms, and they appear to have been associated with a degenerative process — namely, arteriosclerotic disease involving the coronary vessels as well as other vessels in the body. She probably had arteriosclerotic disease in addition to the old mitral lesion.

The pain and stiffness in the back, right leg and both arms and the pain in the chest are general complications that occur in any older patient who is "aching all over." She undoubtedly had degenerative changes in the bones, and I assume that she had hypertrophic arthritis. That could explain the aches and pains that she noted from time to time. The loss of 40 pounds of weight over a period of years, and not just during the year prior to admission, I tie in with generalized arteriosclerosis, chronic intrahepatic splenic disease and possibly inadequate diet, along with some degree of heart failure. She had a smooth tongue, diminished vibration sense and absent ankle jerks. If these findings are correct, they are consistent with vitamin deficiency.

The elevation of the diaphragm on the left can be explained by the enlarged spleen. The heart was enlarged to the left. As I have already mentioned, there was a systolic murmur at the base and a diastolic murmur characteristic of mitral disease at the apex. I suppose that might be an Austin-Flint murmur, but I am inclined to doubt it.

The white-cell counts were consistently low. That is consistent with the chronic intrahepatic disease and splenic enlargement, sometimes called "Banti's disease," although I think that the term should be reserved for those cases that have primary disease in the spleen rather than in the liver. The red cells were hypochromic, a fact consistent with bleeding from the gastrointestinal tract. The nonprotein nitrogen was low, and there was fixation of the specific gravity of the urine — 1.010 to 1.012. Undoubtedly there was renal involvement of a degenerative nature, possibly with infection. On the other hand, a low nonprotein nitrogen is consistent with serious liver disease. The albumin-globulin ratio was approximately 1.0, also suggesting liver disease. The spleen was enlarged both by physical examination and by x-ray. I should like to look at the films. Did any of them show a gallstone or a large mass in the right upper quadrant?

Dr. Milford Schulz: This shadow probably represents a calculus in the lower pole of the kidney.

Dr. Jones: Then I withdraw the remark about gallstones. This picture is quite different and should have been mentioned in the original description of the x-ray findings.

Dr. Joseph Aub: Is the left kidney enlarged?

Dr. Schulz: Both kidneys are good sized, and I do not see any real deformity of the calyxes. All the bones of the pelvis and spine seem to be intact.

The evidence of mitral disease apparently was more prominent when observed fluoroscopically than is shown on the film.

The films of the gastrointestinal tract show an essentially normal stomach, but in the esophagus there are definite varices. I assume that the films of the skull were taken because of the previous head injury or possibly for examination of the bones.

Dr. Jones: From these films it seems to me that there is no reason to change any of the possibilities except to add one as a probability rather than a possibility. I agree with Dr. Aub that the left kidney looks enlarged.

What happened in the hospital is of interest. The patient had an episode of right-sided renal pain with costovertebral tenderness, and I assume that she probably had a calculus, with resulting blood in the urine, fever and chills. Because of that fact it seems reasonable that the shadow in the region of the right kidney is consistent with stone. Is that not correct, Dr. Schulz?

Dr. Schulz: Yes; it seems to be in the lower calyx.

Dr. Jones: The patient had a story of previous renal colic, probably with infection. We know that she eventually developed terminal sepsis and that colon bacilli were found in the urine.

What are the conditions to be found in this woman? I think that she had old rheumatic heart disease with mitral involvement, and probably generalized arteriosclerosis with involvement of the heart. It is quite possible that arteriosclerotic heart disease rather than rheumatic heart disease was of more importance in relation to the heart failure and precordial pain on exertion. She had degenerative changes in the spine. She probably had cirrhosis of the liver with a relatively small liver and an enlarged spleen and resulting portal hypertension and esophageal varices. She did not have a primary hepatoma on top of the cirrhosis. I do not see how one can avoid the evidence of real interference with hepatic function and I do not believe it was entirely on the basis of cardiac failure. She undoubtedly had some changes in the right kidney, probably pyelonephritis as well as arteriosclerotic changes. I do not know the cause of the apparent renal enlargement on the left. There was no hydronephrosis. The ureter was not noted to be enlarged, and on the x-ray films its shadow appears to be normal. Is that correct, Dr. Colby?

Dr. Fletcher H. Colby: From here the renal outline appears to be fairly large but not irregular. There is no depression of the calyxes that I can see. I do not believe that there was a renal tumor.

Dr. Jones: To say that she had a tumor is simply a guess to explain an unusual finding in the kidney. I think that she had right renal colic from a renal calculus, with resulting infection. I do not believe that she had gallstones.

Dr. Aub: Could she not have some widespread degenerative disease, such as amyloidosis?

DR. JONES: I suppose that she could have had amyloid disease. It would not, however, explain the failure to find a large liver. Of course one can have amyloidosis involving only the spleen, but amyloid disease of the liver and spleen, so far as I know, does not give esophageal varices.

DR. REED HARWOOD: The white-cell counts were low.

DR. JONES: Extremely low.

DR. HARWOOD: Is that consistent with cirrhosis of the liver or thrombosis of the splenic vein?

DR. JONES: Yes. It may have been lowered by sulfadiazine, but the initial count was 2200, which was extremely low, and I am sure that counts as low as that occur in cirrhosis of the liver.

CLINICAL DIAGNOSES

Cirrhosis of liver.
Splenomegaly, anemia and leukopenia.
Pyelonephritis.
Left ureteral calculus.

DR. JONES'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis.
Arteriosclerosis.
Cirrhosis of liver.
Pyelonephritis, with right renal calculus.

ANATOMICAL DIAGNOSES

Cirrhosis of liver (toxic type), with splenomegaly.
Esophageal varices.
Ascites.
Thrombosis of portal vein, recent.
Pyelonephritis, right.
Ureterolithiasis, right.
Parathyroid adenoma.
Rheumatic heart disease.
Bone-marrow hyperplasia, erythroid.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed a slightly enlarged heart (490 gm.). There was rheumatic involvement of the mitral, aortic and tricuspid valves — slight to be sure, but definite. The coronary arteries were only slightly sclerotic, so I believe that the heart disease was wholly rheumatic. The liver was slightly enlarged (1900 gm.) and showed a characteristic portal or toxic type of cirrhosis. There were 400 cc. of ascitic fluid. The spleen was tremendous (1600 gm.) and microscopically was fibrous — findings that one sees with the portal hypertension that is the result of cirrhosis. The spleen itself could be called a "Banti spleen," but we usually limit this designation to cases with thrombosis of the splenic vein, which this patient did not have. There was a recent thrombosis, probably a few weeks old, in the portal vein, and the esophagus showed well-marked varices.

Both kidneys were quite large, the right weighing 310 gm., and the left 260 gm. The right contained numerous pinpoint abscesses, and microscopic examination showed pyelonephritis. The pelvis was dilated, and there was a stone in the ureter 5 cm. above the ureterovesical orifice.

An interesting finding was a small adenoma in one of the parathyroid glands, which probably accounted for the renal stones and the resultant pyelonephritis. The low serum phosphorus fits in well with hyperparathyroidism. The bones showed no evidence of osteitis fibrosa, which is not at all unusual since only about half the cases of hyperparathyroidism have bone changes.

The bone marrow showed moderate to marked hyperplasia of the red-cell series.

A PHYSICIAN: In a patient with stones that are due to hyperparathyroidism, is it not unusual to have a normal phosphatase?

DR. CASTLEMAN: No; the phosphatase is elevated in hypoparathyroidism only when there are bone changes.

Erratum. The legend accompanying the cut on page 291 in the March 9 issue of the *Journal* should obviously be deleted.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

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Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

DANGERS OF CONTINUOUS SULFONAMIDE THERAPY

There is a growing tendency to use sulfonamide drugs over long periods of time, particularly for the prophylaxis of certain acute and chronic diseases. This tendency has been encouraged by early reports concerning the reduction of recurrences by the continuous use of sulfanilamide in small groups of patients with rheumatic fever. Further encouragement comes from programs instituted by certain units of the armed forces for the prevention of gonococcal infections or the elimination of meningococcal carriers. Laymen, and physicians too, may consider this use by the armed forces as endorsement of the widespread and promiscuous use of sulfonamide drugs. They are likely to ignore the fact that in the armed forces the drugs are prescribed for special purposes under well-controlled conditions. In most cases a single dose is used or a few doses are given over a period of one to four days. Although such use is not without danger in individual cases, in large groups of people it offers the possibility of reducing the chances of infection or of eliminating a significant proportion of carriers of a highly susceptible organism and thus diminishes the possibility of new cases. At the same time the chances for the development of sensitization are relatively small, provided that the treatment is not frequently repeated at short intervals.

It is known that even small doses of sulfanilamide or related drugs given continuously over long periods often produce significant toxic reactions, including even fatal ones, such as those in which agranulocytosis develops. Furthermore, sensitization may occur, which makes subsequent administration of the drug impossible when it may be required as a life-saving measure. This is true even when such poorly absorbed drugs as sulfaguanidine and succinylsulfathiazole are given over long periods for the prevention of dysentery. Finally, experimental studies in animals have indicated that widespread organic lesions may result from continuous administration of any of the commonly used sulfonamide drugs,[1] and similar pathologic lesions may occur in human beings.

A preliminary report of a recent study by Julianelle and Siegel,[2] of the Public Health Institute of the City of New York, brings up another serious aspect of continuous sulfonamide therapy that has been considered in the past but has not received adequate experimental study — namely, the development of sulfonamide-resistant strains during such treatment These workers made clinical and bacteriologic studies in 30 children who received 1 to 2 gm. of sulfadiazine daily for a period of four months. Thirty comparable children subject to the same environmental conditions but receiving no sulfonamides served as controls. Only mild transient symptoms of toxicity were encountered from the use of the drug. Unfortunately there was a low incidence of respiratory infections both in the treated and in the control children. Nevertheless, both groups had a similar number of colds and minor

respiratory infections, and there was no significant difference in the average duration of illness in the two groups. The total number of organisms recovered in periodic throat cultures made in the sulfadiazine-treated children was not less than that in the controls. Some types of organisms were entirely unaffected by the drugs, whereas others were strikingly reduced in number, particularly the gram-negative cocci (Neisseria). After one month of treatment, however, these organisms again increased, and sulfadiazine-resistant strains were encountered. Similar changes were noted among pneumococci. In the control children many types of pneumococci were encountered continuously throughout the study. In the treated group, on the other hand, the same multiplicity of types was noted at first but within a short time only two types dominated. Tests showed that these two types had become sulfadiazine resistant, and shortly thereafter these same sulfadiazine-resistant strains of pneumococci had spread into the throats of the control group of children, who were housed in the same cottage.

The results of these investigations suggest another possible danger, and a serious one, from the prolonged use of sulfonamide drugs in prophylaxis or treatment. The question is raised whether these drug-resistant virulent strains will eventually lead to infections that are difficult to manage and to control. The development of such strains during the treatment of disease has already been encountered.[3] Julianelle and Siegel correctly point out that further studies are needed to determine whether these drug-resistant strains really constitute a practical hazard in the prolonged use of the sulfonamides.

References

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3. Hamburger, M., Jr., Schmidt, L. H., Sesler, C. L., Ruegsegger, J. M., and Grupen, E. S. Occurrence of sulfonamide-resistant pneumococci in clinical practice. *J. Infect. Dis.* 73:12-30, 1943.

SURVIVAL OF THE FIT

Changes in the environment, sometimes slow, sometimes rapid, and the adaptation of life to them, are being constantly demonstrated, and natural history, so far back as discoverable records go, shows that those forms of life that could not adapt themselves to changes in their surroundings had perforce to perish. The sabre-tooth tiger and the mastodon, once lords of the terrain over which they roamed, are known to us only through crude, prehistoric drawings and an occasional pile of mud-encrusted bones; the giant saurians, maintaining themselves on the lush vegetation of the muck age, succumbed when these conditions changed, and have left us, to remember them by, only their sketetons and a few gigantic footsteps.

It is important to note, however, that no biologic order has completely disappeared from life. We still have tigers and elephants and lizards, but of sizes and varieties and characteristics suited to their continued existence in the medium in which nature has left them, so long as that medium remains suited to them. The working theory of the survival of the fit has seen to it that the correct animal was left to graze in its proper pasture; that a suitable vegetation succeeded in the soil and climate best adapted to it; that those organisms hardy enough to withstand the inimical forces of nature are the ultimate survivors until, perhaps, some new influence will require a greater refinement in the strain or will allow a newly originated species to flourish.

Thus in the vegetable kingdom we find rust-resistant strains of wheat and other food crops and of flowers; blight-resistant chestnuts are appearing, after the apparent destruction of our chestnut stand some years ago. The human race is developing resistance, perhaps owing both to mass immunization and to natural selection, to many of the infectious diseases that have variously scourged it. Syphilis, although still an ubiquitous plague, does not sear as it did when it was first visited on mankind; tuberculosis finds fewer victims and ravages them less fiercely than when consumption took its toll of the last few centuries — an improvement that is not entirely due to better hygiene and to case finding; and measles is a relatively minor annoyance among conditioned populations, as compared with the havoc it can raise on virgin soil, such as existed on Pitcairn and among the Faroe Islanders.

Even as we develop our immunities and our secret weapons for defense, however, our biologic enemies adapt themselves to the new conditions with which

we challenge them, and the battle is never entirely won. Even new and better chemical agents will not furnish the last word against infectious disease, valuable as they have proved themselves to be, for the human body may become sensitized to them, and drug-resistant strains of various pathogenic organisms put in their appearance. Cases of pneumococcal pneumonia are encountered, for example, that do not respond to sulfonamide therapy, and the incidence of gonococcal infections that are resistant to chemotherapy is appreciable. The same, no doubt, will be true with penicillin and every other agent that we may develop. The struggle is unremitting.

MEDICAL EPONYM

Darier's Disease (Pseudoxanthoma elasticum)

Jean Darier (b. 1856), of Paris, presented a paper "Pseudoxanthoma elasticum" at the Third International Dermatological Congress in London during August, 1896. A German translation of this paper, by Dr. Turkheim, of Hamburg, appeared in the *Monatshefte für praktische Dermatologie* (**23**:609-617, 1896). A portion of the translation follows:

> There is a disease of the skin, apparently of rare occurrence, with clear, unmistakable anatomic and clinical symptoms that can be termed "pseudoxanthoma elasticum."
>
> This disease expresses itself clinically by the formation of macules, plaques or yellowish papules that have great similarity to those of true xanthomas.
>
> Anatomically, the disease finds its expression in a disruption with swelling and finally disintegration of the elastic tissue into absolute crumbs. . . . On the other hand the specific metamorphoses of xanthoma, xanthomatous cells and fat granules are missing.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE TO AID THE DISTRICT RATIONING OFFICER

Requests for extra rations on medical certificates of patients' necessity, above and beyond the basis levels to which the population as a whole has cheerfully submitted, continue to come in to the local rationing boards at a fairly steady rate. Those that exceed certain established maximums or concerning which any particular question is raised are usually referred to the regional Office of Price Administration to be passed on by the advisory medical committee.

Some rationing boards, such as the Brookline board, have appointed local medical advisory committees; such a course, if widely followed, would serve to lighten considerably the load of the regional office, especially if existing formulas were accepted in a spirit of co-operation. It must be re-emphasized that the advisory committee of the Massachusetts Medical Society is desirous only of helping to apply the principles of food rationing in such a way that as little hardship as possible will be inflicted on anyone. Furthermore, it believes that basic rationing as it applies to the majority of persons carries no hardship.

It has been possible at last to obtain reasonably accurate figures on the number of persons obtaining extra ration allowances from one large community — Somerville. In that city, 0.5 per cent of the population is receiving supplementary food allowances — on the whole, not a staggering proportion of the residents.

The alluring diagnosis of anemia is assuming increasing prominence as a reason for the prescription of extra rations, especially red meats and liver. In reference to this situation, it must be pointed out that anemia is not included in the legitimate extra-point diseases listed by the Subcommittee on Medical Food Requirements of the National Research Council; that hematologists have ventured the opinion that iron and liver extract are more effective antianemic substances than is meat; and that in England liver is considered too precious to use as food, being reserved for the preparation of liver extract for the treatment of hyperchromic anemia.

Joseph Garland, *Chairman*

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

WEISSMAN — Robert J. Weissman, M.D., of Bristol, died February 1. He was in his thirty-third year.

Dr. Weissman received his degree from the University of Vermont College of Medicine in 1937. He first interned in Louisville, Kentucky, before setting up a practice in Richmond and Montpelier, Vermont. Dr. Weissman had been in Bristol about three years.

His widow and mother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

Clinic	Date	Clinic Consultant
Salem	April 3	Paul W. Hugenberger
Haverhill	April 5	William T. Green
Lowell	April 7	Albert H. Brewster
Springfield	April 12	Garry deN. Hough, Jr.
Brockton	April 13	George W. Van Gorder
Pittsfield	April 17	Frank A. Slowick
Worcester	April 21	John W. O'Meara
Fall River	April 24	Eugene A. McCarthy
Hyannis	April 25	Paul L. Norton

MISCELLANY

WARREN TRIENNIAL PRIZE

The Warren Triennial Prize, which was founded by the late Dr. J. Mason Warren in memory of his father and which carries an appreciable honorarium for the best dissertation, considered worthy of a premium, on some subject in physiology, surgery or pathology, was recently awarded by the General Executive Committee of the Massachusetts General Hospital to David G. Cogan, M.D., V. Everett Kinsey, Ph.D., and Erwin O. Hirsch, B.A., for their essay entitled "Physiologic Studies on the Cornea." The paper "Studies on Traumatic Shock," by Everett I. Evans, M.D., received honorable mention.

CORRESPONDENCE

ATHEROSCLEROSIS

To the Editor: How difficult the task of making plain to the generality of the profession the significance of retained cholesterol esters is going to be is indicated by the reaction of a brilliant man like Dr. Roger I. Lee (Geriatrics: The medical care of the elderly. *New Eng. J. Med.* **230**: 190-193, 1944) to the thesis that this agent is the cause of atherosclerosis. Let me say in the beginning that the term "atherosclerosis" is not mine. Recognition of the distinctive character of the disease goes back to Virchow and Aschoff. The contradictory name atherosclerosis (literally, mushy hardening) goes back to Marchand. The term is not limited in its application to "premature and devastating arteriosclerosis." It is applied to the important form of arteriosclerosis that is probably responsible for at least 90 per cent of clinical and pathologic manifestations of arteriosclerosis as such.

The sterols are evidently necessary to life since they are found in all living cells, animal and vegetable. Cholesterol is one of the most complex substances found in the animal body (Schoenheimer). It is so complex that we do not know how it is metabolized. We do know, however, that its metabolism is difficult, and that when the substance is present in excess it is precipitated in crystalline ester form in the tissues and is treated as a foreign body. It is engulfed by phagocytic cells and is carried in these cells into the arterial intima. The characteristic that differentiates atherosclerosis from other forms of arterial disease is the presence in its lesions of crystals of excess cholesterol, usually in ester form, and visible under polarized light. We do know that excess ester cholesterol is a chronic irritant comparable to silica sol. We do know that excess cholesterol satisfies all of Koch's postulates as the cause of atherosclerosis.

Dr. Lee makes much (or little) of the use of the rabbit for experimental purposes. The old criticism that the rabbit suffers an artificial disease because we introduce into its diet an animal fat to which it is not accustomed does not carry much weight when one remembers that much of the knowledge we have of human infection and immunity arose from the introduction into rabbits of bacteria or toxic agents to which they were not accustomed. It is also to be remembered that the rabbit synthesizes this same animal fat (cholesterol) for the needs of its own cells. Moreover atherosclerosis has been produced in chickens by adding excess cholesterol to their diet (Dauber, D. V., and Katz, L. N. Experimental cholesterol atherosclerosis in an omnivorous animal. *Arch. Path.* **34**:937-950, 1942). As a matter of fact the principal function of rabbit experimentation has been to satisfy Koch's postulates and to clear up the modus operandi of excess cholesterol activities. Our basic knowledge of the causation of the disease is due to the study of the specific relation of excess cholesterol esters to the lesions of human atherosclerosis, and is particularly due to the following of the disease sequence (Sydenham's footsteps of disease) from beginning to advanced stages in some thousands of human lesions.

Cholesterol is the forerunner of the cortical adrenal secretion. It is the probable source of the bile acids and the sex hormones. Its degradation products include known carcinogens. A retained excess of cholesterol is potentially dangerous. There is evidence of its pathogenic action in the human body in addition to the causation of atherosclerosis. Excess cholesterol is manifestly a substance that should be destroyed or excreted. We are able to metabolize it in youth, as is shown by its removal from the ester deposits in the aorta in the atheromas of infancy and puberty. It is this ability that prevents the production of atherosclerosis in the arteries of youth.

As we age we lose the power to control cholesterol. There is no longer a metabolism that can destroy the excess, and no excretory machinery that can remove it from the body. It remains within the body and is responsible for the production of the condition that led Dr. Lee to conclude: "No, that isn't wear and tear; that is just rust." Modern industrial chemistry is demonstrating new methods to prevent rust. It is my expectation that modern medical methods, no longer influenced by the "abandon hope" attitude adopted in so-called "modern" texts on geriatrics, will find means of preventing or controlling the "rust" that can kill men even in the twenties and thirties from coronary disease, and can lift cardiovascular renal disease and cancer to a position of domination of the causes of death as early as the forties.

TIMOTHY LEARY, M.D.

784 Massachusetts Avenue
Boston

CANDIDATES FOR INTERNSHIPS

To the Editor: At a recent meeting of the War Participation Committee of the Massachusetts Medical Society, Dr. Edward A. Knowlton, of Holyoke, raised an important question. He asked how hospitals approved for intern training should attempt to procure interns.

Under the accelerated program and the 9–9–9 plan, nearly all medical students who are in their final year, expecting to graduate in the fall of 1944, have been appointed to internships that will begin about October 1 and will end about July 1, 1945. A number of hospitals already are beginning to scrutinize, as potential intern candidates to succeed them, third-year medical students, who so far have had no more than a few months' exposure to clinical work of any sort.

The Boston Interhospital Internship Committee has decided to hold on October 16 to 19, 1944, its examination for the next group of internships available under its jurisdiction. This committee considers it unsound to examine any candidates until they have completed at least three full terms of medical education. Not before then can they be expected to have had enough clinical work to be in a position to know the type of internship that they wish to undertake; and not before then can their teachers have a valid opinion concerning their ability as clinicians.

The internship is such an important part of medical education and interns are such an essential part of hospital efficiency that their proper selection under war conditions is a most important step. Their premature appointment is unnecessary and does not seem sensible.

REGINALD FITZ

319 Longwood Avenue
Boston

"HOLMES AS A PSYCHIATRIST"

To the Editor: My attention has been called to two misstatements in the editorial *Holmes as a Psychiatrist*, published in the February 3 issue of the *Journal*.

The first relates to the date of the address given by Holmes before the Phi Beta Kappa Society at Harvard. The date used, 1871, was based on a statement by Oberndorf in his essay *The Psychiatric Novels of Oliver Wendell Holmes*. Actually the lecture was given on June 29, 1870, as clearly stated on the title page of the printed address, which was not published until 1871. Editions were issued in both Boston and London in that year, and the address was reprinted, with a new title page, in Boston in 1872.

The editorial stated, moreover, that the address, "was withheld from publication for more than twenty years, and only after careful revision, expansion and annotation had taken place, did Holmes allow it to appear in print." As noted above, this statement is entirely incorrect. The address was printed not only once but a number of times, and apparently Holmes made no effort to suppress it himself. We are indebted to Mr. F. Franklin Currier, the bibliographer of Holmes, moreover, for calling attention to a statement by Holmes in a letter to a classmate: "The sale and reception of my little book have been quite a surprise to me, for I hardly expected it to pay for itself but so far it has done remarkably well."

The writer of the editorial misinterpreted a statement by Oberndorf, who wrote that the essay "was carefully revised, expanded, and annotated before it was printed in *Pages from an Old Volume of Life*." This reference should have been verified and not taken to mean that the address was not published immediately after it was given. Oberndorf, moreover, is not correct in saying that the address was "revised, expanded, and annotated" before it was printed. Even in the 1883 edition of *Pages from an Old Volume of Life*, the article contains few revisions.

I am indebted to Dr. George R. Minot for calling my attention to these errors.

HENRY R. VIETS, M.D.

262 Beacon Street
Boston

(*Notices on page x*)

SUPPORT FOR THE FAILING HEART... *Digalen 'Roche'*

NOTICES

CHILDREN'S HOSPITAL

On Thursday, March 30, at 5 o'clock, in the amphitheater of the Children's Hospital, Dr. Cecil K. Drinker will speak on the subject "The Application of Pulmonary Physiology to Therapeutic Procedures with Special Reference to the Use of Oxygen."

This meeting is open to the public.

BOSTON DISPENSARY

A clinical staff meeting of the Boston Dispensary will be held at the Pratt Hospital Auditorium on Thursday, April 6, at 12:30 p.m. Dr. Samuel R. Meaker will speak on the subject "Some Practical Details of the Management of Sterility." Luncheon will be served at 12 noon.

All interested persons are invited to attend.

WASHINGTONIAN HOSPITAL

A lecture on the treatment of alcoholism will be given jointly by Dr. Robert Fleming and Dr. Joseph Thimann on Friday evening, April 7, at 7:30, at Zero Marlborough Street. Dr. Fleming will cover the general subject "The Treatment of Chronic Alcoholism," and Dr. Thimann will speak on the topic "The Plan of Treatment at the Washingtonian Hospital, with Special Consideration of the Conditioned Reflex Treatment." This is the fourth in a series of lectures on alcoholism being given under the co-sponsorship of the Washingtonian Hospital and the Committee on Alcoholism of the Boston Council of Social Agencies.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, April 6, at 7:15 p.m. in the classroom of the nurses' residence. Dr. Sallie Saunders will speak on the subject "The Emergency Maternity and Infant Care Program." Dr. R. Adelaide Draper will be chairman.

AMERICAN BOARD OF OPHTHALMOLOGY

The officers of the American Board of Ophthalmology for 1944 are as follows: chairman, Dr. John Green, St. Louis; vice-chairman, Dr. Frederick C. Cordes, San Francisco; secretary-treasurer, Dr. S. Judd Beach, Portland, Maine; assistant secretary, Dr. Theodore L. Terry, Boston; consultant, Dr. Walter B. Lancaster, Boston.

All correspondence to the Board should be addressed to the secretary's office, 704 Congress Street, Portland, Maine.

WAR CONFERENCE ON INDUSTRIAL MEDICINE, HYGIENE AND NURSING

The Second War Conference of industrial physicians, industrial hygienists and industrial nurses will be held in St. Louis, May 8 to 14, 1944, at the Hotel Jefferson. The participating organizations are the American Association of Industrial Physicians and Surgeons, the American Industrial Hygiene Association, the National Conference of Governmental Industrial Hygienists and the American Association of Industrial Nurses.

The medical subjects to be presented include welding in relation to clinical aspects and control of hazards; medical phases and means of prevention of noise; better health in small plants; the industrial physician's opportunity to advance medical knowledge; maladjustment and job environment; women in industry; and panel discussions on "Who Can Work?" and other timely questions. Two clinics, one surgical at the Barnes Hospital and the other medical at the Desloge Hospital, will be featured among the morning sessions.

The industrial hygienists and the industrial nurses will consider various timely and important topics.

This conference will present an unequaled opportunity for everyone interested to any degree in industrial-health problems — especially those of present wartime exigencies — to hear them discussed by the recognized experts in all departments of this important and growing field.

Those desiring accommodations at the Hotel Jefferson should communicate immediately with John Reinhardt, War Conference Housing Bureau, Syndicate Trust Building, St. Louis, Missouri.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Wednesday, June 7, through Tuesday, June 13, 1944. The Hotel William Penn in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the hotel.

Candidates for re-examination in Part II must make written application to the secretary's office not later than April 15.

The Pittsburgh Obstetrical and Gynecological Society will hold an informal subscription dinner meeting at the Hotel William Penn on Saturday evening, June 10, at 7:00 p.m. Candidates are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, secretary, 121 University Place, Pittsburgh 13.

The Office of the Surgeon General of the United States Army has issued instructions that men in service who are eligible for Board examinations should be encouraged to apply and that they may request orders to detached duty for the purpose of taking these examinations. Candidates in the Army or Navy are requested to keep the secretary's office informed of any change in address.

Deferment without time penalty, under a waiver of the published regulations applying to civilian candidates, will be granted if a candidate in service finds it impossible to proceed with the examinations of the Board. Applications are now being received for the 1945 examinations. For further information and application blanks, address Dr. Paul Titus, secretary, 1015 Highland Building, Pittsburgh 6.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, March 30

Thursday, March 30

*9:00–10:00 a.m. Medical clinic. Dr. S. J Thannhauser. Joseph H. Pratt Diagnostic Hospital.

12:30 p.m. Annual meeting and luncheon, Boston Health League. College Club, 40 Commonwealth Avenue, Boston.

†5:00 p.m. The Application of Pulmonary Physiology to Therapeutic Procedures with Special Reference to the Use of Oxygen. Dr. Cecil K. Drinker. Amphitheater of the Children's Hospital.

Friday, March 31

*9:00–10:00 a.m. Present Status of Penicillin. Dr. Donald G. Anderson. Joseph H. Pratt Diagnostic Hospital.

Saturday, April 1

*10:00–11-30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, April 3

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, April 4

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, April 5

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.
†Open to the public.

March 29. Tufts Medical Alumni Association. Page 302, issue of March 9.

March 30. Boston Health League. Page xi. issue of March 16.

April 6. Boston Dispensary Clinical Staff Meeting. Pratt Hospital auditorium. Notice elsewhere on this page.

April 6. New England Hospital for Women and Children. Notice elsewhere on this page.

April 7. Lecture on the treatment of alcoholism. Co-sponsorship of the Washingtonian Hospital and the Committee on Alcoholism of the Boston Council of Social Agencies. Notice elsewhere on this page.

April 13. The Use and Misuse of Bacterial Chemotherapy. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

(*Continued on page xiii*)

NOTICES (*Continued from page x*)

MAY 8-14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

JUNE 7-13. American Board of Obstetrics and Gynecology. Page x.

JUNE 12-16. American Medical Association. Annual meeting, Chicago. Page 798, issue of November 18.

JUNE 12-16. American Physicians' Art Association. Page x, issue of March 2.

OCTOBER 3-5. American Public Health Association. Hotel Pennsylvania' New York.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

MAY 4. Censors' Meeting. Page xiii, issue of February 10.

WORCESTER

APRIL 12. Hahnemann Hospital, Worcester.

MAY 10. Annual meeting.

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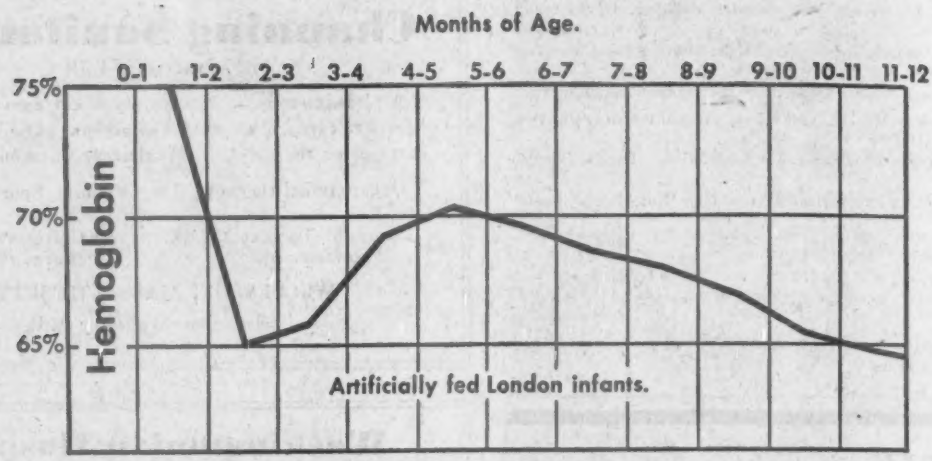

NUTRITIONAL ANEMIA IN INFANTS

The consensus is that it is important for infants to receive generous additions of iron during the first 6 months. This chart, adapted from Mackay,[1] shows the reason for the need of iron supplements.

REASONS FOR EARLY FEEDING OF PABLUM (OR PABENA)

1. The infant's initial store of iron is rapidly depleted during the first months of life. (Mackay,[1] Elvehjem[2]). About 30% of the iron freed from the hemoglobin during the first two months is lost, and while hemoglobin destruction takes place, all infants are in negative iron balance. (Jeans,[3] and Usher, et al.[4]).

2. During the early months of life the infant obtains very little iron from milk — 1.44 mg. per day from the average bottle formula of 20 ounces or possibly 1.7 mg. per day from 28 ounces of breast milk. (Holt,[5] Jeans[3]). The incidence of nutritional anemia has been found to be high among infants confined largely to a diet of cow's milk. (Davidson, et al.[6] Usher, et al.,[4] Mackay[1]).

For these reasons and also because of the low hemoglobin values so frequent among pregnant and nursing mothers (Strauss,[7] and Gottlieb and Strean[8]), the pediatric trend is constantly toward the addition of iron-containing foods at an early age, both to normal infants and those with pylorospasm. (Neff,[9] Blatt,[10] Brennemann,[11] Monypenny[12]).

THE CHOICE OF THE IRON-CONTAINING FOOD

1. Many foods high in iron actually add very little to the diet because much of the mineral is lost in cooking or because the amount fed is necessarily small or because the food has a high percentage of water. Strained spinach, for instance, contains only 1 to 1.4 mg. of iron per 100 Gm. (Bridges[13]).

2. To be effective, food iron should be soluble. Some foods fairly high in total iron are low in soluble iron. Thus egg yolk and liver have less soluble iron than does farina, which is very low in total iron. (Summerfeldt[14]). Oxalate-containing leafy vegetables are low in soluble iron and appear not to be well utilized as a source of iron by infants. (Kohler, et al.,[15] and Stearns[16]).

3. **Pablum (and Pabena) are high both in total iron (30 mg. per 100 Gm.) and soluble iron (7.8 mg. per 100 Gm.) and can be fed in significant amounts at an early age, without digestive upsets. (Blatt,[10] Monypenny[12]). Clinical studies of sick and well babies have shown Pablum to be of value in raising hemoglobin values (Crimm, et al.,[17] Summerfeldt and Ross[18]), even when egg yolk and spinach were not effective (Stearns[16]).**

Pablum, a palatable mixed cereal food, vitamin and mineral enriched, and cooked thoroughly and dried, consists of wheatmeal (farina), oatmeal, wheat embryo, cornmeal, powdered beef bone, sodium chloride, alfalfa leaf, brewers' yeast, and reduced iron. (The oatmeal form of Pablum is called Pabena.)

[1-18] Bibliography on request.

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